ANNUAL REPORT
OF
PROGRAM ACTIVITIES

NATIONAL INSTITUTES OF HEALTH

1967 - 1968

NATIONAL INSTITUTE OF NEUROLOGICAL
DISEASES AND BLINDNESS
VOLUME II

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ANNUAL REPORT of Program activities
July 1, 1967—June 30, 1968
Associate Director for Collaborative and Field Research
National Institute of Neurological Diseases and Blindness
National Institutes of Health

Introduction

The Collaborative and Field Research programs are concerned in large part with projects under development. These new activities are subject to extensive, detailed reviews, and are dependent upon the acquisition of new funds. In times of economic stringency, the establishment of new projects is fraught with difficulty. Although areas of pressing need have been identified, and projects designed to meet these needs, the actual investigations will have to be deferred or progress slowly until increased allocations are available. In view of the preceding, it is appropriate to cast this summary in the form of a balance sheet—positive and negative, rather than the traditional program-by-program summary.

Program Accomplishments—FY 1968

Studies of slow, latent, and temperate virus infections and related developmental studies have gone well. Further inoculation of primates has proved early findings to be accurate and is providing excellent material for microbiological studies. Of particular significance is the successful transmission of Jakob Creutzfeldts disease (subacute spongiform encephalopathy) to the chimpanzee, further implying the existence of an agent in these diseases. The collection and neuroanatomical study of whole brains in collaboration with the Harvard Medical School is another important step in this program, developing new data in the field. The successful collection of new human material for viral studies from patients with Kuru in the New Guinea highlands has continued as a field activity. In addition, epidemiologic data continues to be assembled on this unique disease.

The Epidemiology Branch has succeeded in completing some significant studies on the incidence and prevalence of neurologic and sensory diseases. Studies of penicillin therapy in general paresis have indicated a variability in its effectiveness in arresting this expression of neurosyphilis. Certain neurologic symptoms seen in cancer patients and previously attributed to the presence of cancer have been noted with regularity in patients suffering a variety of other non-malignant chronic diseases, implying that the cause of these symptoms was the general health of the patient, not cancer. Techniques utilizing lymphocytes have been developed for the study of immunologic mechanisms that may play a part in multiple sclerosis. Genetic studies of dystonia musculorum deformans have revealed that there may be two forms of this comparatively rare disorder. Epidemiologic and genetic studies of amyotrophic lateral sclerosis and Parkinsonism-dementia on Guam continue.

The need for a Pathology Branch within the Collaborative and Field Research program area has been identified. Its primary function would be to provide adequate backup for studies of degenerative diseases on Guam, studies of slow

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and latent virus infections, and studies in primate physiology. Competent leadership and staff for this activity are available if NINDB can make funds and facilities available.

In July, 1967, ophthalmic examinations of twins on a registry maintained by the Epidemiology Branch began. Since then, over 375 pairs of twins have received a thorough screening examination. Carefully planned studies utilizing this population will begin in FY 1969.

The formidable task of constructing a physical model of the head in order to study various forces of injury and their effect upon the head has begun. Three contractors have undertaken the project by determination of the physical properties of the tissues of the head. This unique research, combining the sophisticated techniques of biology and engineering will continue for several years, culminating in the development, construction, and experimental loading of physical and mathematical models. This program is under continual review of an expert committee.

The selection, location and contact of a large population of veterans who sustained head injuries in the Korean campaign has been completed. A matched control population has also been selected. This project has been accomplished in collaboration with the National Research Council Follow-up Agency and appropriate agencies of the Department of Defense. Concise work-ups of medical information on these veterans has been completed. From this information, the American National Red Cross, Service to Military Families, is conducting a field contact study. This population provides an imposing resource for clinical studies of the late effects of head injury.

A current registry of head injuries taking place in Viet Nam is maintained in cooperation with the Surgeons General of the Departments of the Army, Navy and Air Force.

Through the efforts of staff and consultants, the publication of an abstract journal in epilepsy, Epilepsy Abstracts, has gotten underway. Six editions of the first volume have appeared in print, and have been well-received by the scientific community.

A promising start has been made in the initiation of a program for the development and marketing of more effective anticonvulsant drugs. After considerable staff planning, the first research contract for systematic clinical trials of a new drug has been negotiated. Fresh channels of communication have been opened between basic pharmacologists and the drug industry via a symposium sponsored by NINDB and held in Salt Lake City in May, 1968. The proceedings of this meeting will be published in Epilepsia in the near future. This anticonvulsant drug program has been recognized by NINDB and NIH as a program for future expansion and acceleration.

With the encouragement and support of the PHS Advisory Committee on the Epilepsies, a symposium on the Basic Mechanisms of the Epilepsies is scheduled for November, 1968. A preliminary workshop for participants was held in February. The published proceedings of this meeting should provide a new impetus to basic research in epilepsy.

Program Limitations—FY 1968

A significant factor in 1968 was a static budget. There were minimal increases in available positions and no increases in funds in the FY 1968 budget. There are no increases anticipated for FY 1969. These seriously restrict program development.

The disapproval of continuation grants for the Collaborative Study of Epilepsy has created program dislocation in a crucial area. The four collaborating investigators had applied for support for a third year of the planning phase. These applications were disapproved by Study Section and Council with a recommendation to complete this planning phase by December 31, 1968, including the development of definitive hypothesis to be tested in a subsequent phase if support could be obtained. A major reason for the continuation request was to accomplish the preceding without loss in assembled staff or patient population. There will now exist a crippling hiatus between studies.

Orderly progress of studies of the late effects of head injury was disrupted by two adverse actions: (1) a large-scale collaborative study of the head-injured veterans of the Korean campaign and controls was disapproved by an ad hoc NINDB review panel in January, 1968, and (2) the NINDB Directorate deferred consideration of a modest proposal to utilize part of this large population for the study of the posttraumatic syndrome. These two actions delay an attack on an important and neglected aspect of craniocerebral trauma. This delay compromises the utilization of a unique study population, and the scientific resources currently available to carry out these studies.

The termination of the research contract with Cornell Aeronautical Laboratory, Inc. for support of a pilot study of the incidence and nature of head injury dislocated an activity that was carefully planned and partially implemented. The termination of the project in the name of economy seriously impairs rational progress and meaningful appraisal of head injury as a health problem.

Although progress has been made, and will continue to be made, the setbacks of the past year will have to be confronted and corrected if the overall objectives of the collaborative programs involved are to be attained. The Collaborative and Field Research program looks forward to the resolution of these problem areas, the occupancy of space in Building 36, the initiation of primate physiology research, and the resumption of normal and necessary program growth in FY 1969 and the years ahead.

CONTRACT NARRATIVE
Office of the Associate Director—Collaborative and Field Research
July 1, 1967—June 30, 1968

COLUMBIA UNIVERSITY (PH 43-66-36)

Title: Study of the Mammalian Brain under Various Conditions

Contractor's Project Director: Dr. H. Houston Merritt

Current Annual Level: $80,000

Objectives: To study functional and structural alterations in the central nervous system of primates under varying conditions.

Major Findings: The results of an investigation of the effects of x-irradiation on the cerebral cortex were published in a special issue of Brain Research in January, 1968.

The first functional alteration observed was a decrease in voltage of the evoked response from the visual cortex at 4 to 12 weeks post irradiation. Roughly coincident with this was an alteration in the neuropil, beginning with a decrease in the basilar dendrites, followed in turn by an alteration in spines, a reduction in apical arborization and a loss in cell bodies. These alterations progressed throughout the experimental period.

The relative depression in amplitude slowly diminished until approximately the eighteenth week, at which time both sides showed an equal response somewhat lower than that in the initial recordings. By 26 weeks, a second wave of right side depression, more severe than the first and accompanied by delta and theta activity, began. At about the same time, 28 to 44 weeks, the histological changes included destruction of neuronal tissue, with severe disorganization of cyto- and myeloarchitecture, accompanied by glial, inflammatory and vascular reactions.

Significance to NINDB Program and Biomedical Research: This project has demonstrated some of the significant events in the central nervous system following ionizing irradiation. Studies are now underway to develop further information on the underlying mechanisms of brain function in the macaca mulatta from a developmental point of view.

Proposed Course of Contract: This contract will continue in effect, supporting ongoing studies. As soon as laboratory space in Building 36 is available, the project will be assimilated into the on-campus activities of the Collaborative and Field Research program, and the contract will be terminated.

ANNUAL REPORT
July 1, 1967—June 30, 1968
Child Growth and Development, Disease Patterns of Primitive Cultures, and Slow, Latent and Temperate Virus Studies
Office of the Associate Director—Collaborative and Field Research
National Institute of Neurological Diseases and Blindness
National Institutes of Health

The program of the Section for the Study of Child Growth and Development and Disease Patterns in Primitive Cultures, and the Laboratory of Slow, Latent and Temperate Virus Infections, though encompassing many diverse projects, effectively operates as a unit. Much of the unification of the program derives from the study of the disease kuru and other diseases, many involving the nervous system, which occur in unusual frequency or form in isolated populations. Our long-term studies of child growth, development and behavior and disease patterns in primitive, isolated and migratory populations have greatly influenced 1) the Program for the Study of Human Adaptability in primitive groups which is the human biology focus of the International Biological Program, and 2) the World Health Organization recommendations for the Study of the Population Genetics of Primitive Groups, which was again revised at the Geneva meetings of the Expert Committee in September 1967, at which we were represented.

The program has continued to integrate work in primitive cultures with studies on learning and development and on human adaptability and genetics with studies on slow, latent and temperate virus infections and other microbiological studies, immunological studies on the nature of the immune and hyperimmune response in man, and neuroanatomical studies on variations in the human brain.

Kuru in New Guinea remains the focus of attention, since it has provided the first and most profitable animal model we possess of a subacute degenerative disease of the nervous system of man caused by a slow virus. Transmission of the disease from human visceral tissue, as well as brain, has been repeatedly accomplished, and the characterization of the infectious agent involved has been a principal activity of the laboratory. With over seventy virus agents isolated from tissue explants from chimpanzees with experimental kuru, it becomes an enormous task to identify which, if any, of these plays an etiological role in the disease. For that reason, explant cultures were prepared during the prolonged expedition to New Guinea from brain and other tissues of kuru victims autopsied within an hour of death, and these have been successfully brought to our laboratory where they are being maintained and are the source of material for chimpanzee inoculation, electron microscopic and fluorescent antibody study and attempts at isolation of latent or masked viruses.

Field epidemiology of kuru this year showed further evidence of increasing age of youngest kuru victims with the disappearance of cases in early childhood. The overall kuru incidence is about one-third lower than in the early years of study. The possibility that cannibalism has been the major mode of spread of kuru now seems highly probable and whether within the human species genetic susceptibility is important is now doubtful. Feeding experiments in chimpanzees have only been on for three years. Epidemiological data would suggest an incubation period on oral infection of five to fifteen years or more. There is some evidence to suggest that vertical transmission from mother to offspring may not be occurring and that oral infection from eating the brain and other viscera of dead kuru victims was the main mode of kuru spread. The continued "brain passage" which such endocannibalism of brain tissue implies may have even contributed to the selection of a neurotropic variant of a common virus and thus originated kuru.

Study of the kuru virus has demonstrated its filterability, serial transmissibility in the chimpanzee, presence in visceral tissue other than brain, presence in brain in titers of at least 10^6 infectious units per ml., infectivity by peripheral (non-intracerebral) routes of inoculation, and shortened incubation period on passage.

Scrapie, mink encephalopathy, visna and other slow virus infections causing subacute degenerative diseases of the nervous system are being used as additional animal models in the program. Other slow infections of animals not primarily involving the central nervous system, such as maedi and Montana sheep disease (both of which may be pulmonary forms of a visna virus infection) and Aleutian mink disease and late disease in persistent tolerant infection with lymphocytic choriomeningitis virus are also under study.

Kuru served to bring scrapie disease and scrapie virus to the attention of medical science in this country. A similar analogy to that of kuru with scrapie was early drawn between kuru and Creutzfeldt-Jakob syndromes in man. Spongiform encephalopathy of gray matter in Creutzfeldt-Jakob syndrome very closely suggests the extensive spongiform encephalopathy of gray matter seen in chimpanzees with experimental kuru. Brain biopsy material from one human patient with spongiform encephalopathy of the Creutzfeldt-Jakob type has now produced a fatal subacute spongiform encephalopathy in a chimpanzee after fourteen months' incubation with pathology in the chimpanzee resembling that in the patient and distinguishable from that of experimental kuru in the chimpanzee. Therefore, a large study of Creutzfeldt-Jakob syndromes is under way, and we are intensifying our interest in presenile dementia (Pick's and Alzheimer's disease), and in senility itself.

On learning of the identification by French workers of tubular structures suggesting a myxovirus in the inclusion bodies of brain cells in subacute sclerosing panencephalitis (Dawson's subacute inclusion encephalitis) we intensified our virological investigations of this disease with resulting discovery of a specific hyperimmune response to measles virus in serum and cerebrospinal fluid. We also intensified our attempts to isolate the virus from human brain biopsy or early autopsy material. When evidence that a slow measles infection or a persistent and masked measles infection was causing this disease was accumulating in many laboratories, we called

together with Dr. Wolfgang Zeman and Dr. John L. Sever, a special symposium on the disease at the NINDB, the proceedings of which have already been published as a Supplement to NEUROLOGY. Our subsequent work reveals that a hyperimmune response to measles virus may be of diagnostic importance in the disease; that the disease is of much higher frequency than that previously suspected; and further incriminates the measles virus as the causitive agent of its disease, probably largely in an incomplete virus form which cannot be cultivated in vitro or masked by gammaglobulin neutralizing antibody which is deposited in the neurons. Attempts to transmit or identify virus directly or indirectly in many other subacute degenerative nervous system disorders are in progress; these include studies on multiple sclerosis, amyotrophic lateral sclerosis, dementia-Parkinsonism, Parkinson's disease, Schilder's disease, Werdnig Hoffman disease, and others.

The intensive study of human isolated primitive populations from a general human biological approach has been continued. It involves selected populations in Micronesia, Melanesia (especially New Guinea), Polynesia and South America (Indian groups), and to a lesser extent, isolated primitive populations in Asia and Africa. Genetic studies of gene drift continue with an attempt to correlate multiple polymorphisms with disease patterns and growth patterns. Growth studies, particularly with the Anga people, formerly called the Kukukuku of New Guinea, indicate an extreme delay in menarche and male puberty in these short-statured people, and a very atypical post-pubertal growth pattern with premature aging.

When brain specimens are available from these population isolates, they are used in our studies of neuroanatomical variations in the human brain. Certain isolated groups have already demonstrated unusually large septal nuclei, massa intermedia, and lateral geniculate bodies; unusual thalamic nuclei; the presence of precommisural fornix fibers; unusually shaped and small frontal lobes; unusual configuration of cortical sulcci and gyri; and small brain weight. We have collected over one hundred fifty brain specimens from diverse ethnic groups for this study, the neuroanatomical aspects of which are being studied by Elisabeth Beck of London, with the assistance of the Warren Anatomical Museum at Harvard, and by Dr. Rolf Hassler and Dr. Heinz Stephan of Max-Planck-Institut für Hirnforschung in Frankfurt, Germany.

In the immunologically virgin populations which we have encountered among the isolated groups studied, investigations of immune response to measles, influenza, and to measles vaccine and monovalent influenza vaccines has continued. Results indicate that this long-term study will be a crucial one in the evaluation of immune response of man to both measles and influenza virus antigens. These isolated populations are also providing data on the antigenic structure of old influenza strains, some as early as that of the 1965 influenza pandemic. One of the island populations has been found to be virtually free of tozoplasmin antibody; another atoll to have a remarkably high incidence of amoebiasis by serology and stool examination, and to have many more deaths from amoebic liver abscesses than occur in other atolls.

During the current field expedition to New Guinea and Melanesia further work was completed in the analysis of gestural communication in several of the groups under study, cinema and tape recording have been

extensively used, and a catalogue of gestural language is being compiled in an attempt to analyze emblematic and other forms of non-verbal communication in these cultures. Comparative psychosexual development of three New Guinea groups which have amazingly different approaches to child rearing, has continued to be contrasted in a study now of eleven years' duration. These three groups reveal, in close proximity, the most extreme divergencies in psychosexual maturation we know of in the world. Study of cognitive style as it influences symbolic bahavior in language, drawing, movement, gesture and dance is a further focus of our attention in primitive groups. It has already revealed markedly different patterns of thought, learning, and quantitative reckoning.

CONTRACT NARRATIVE

Child Growth and Development, Disease Patterns of Primitive Cultures, and Slow, Latent and Temperate Virus Studies
Office of the Associate Director-Collaborative and Field Research
July 1, 1967-June 30, 1968

HARVARD UNIVERSITY (PH 43-68-78)

Title: Studies of the Structural Variability of the Human Brain

Contractor's Project Director: Dr. Richard L. Sidman

Current Annual Level: $54,500

Objectives: To conduct neuroanatomical and neuropathological research in support of studies of slow, latent and temperate virus infections in man and animals, and of studies of the structural variability of the human brain.

Major Findings: This contract was awarded January 1, 1968, therefore findings to date are preliminary. Approximately fifteen whole brains among the many collected by Dr. Gajdusek and his associates have been serially sectioned, using techniques developed by Drs. Yakovlev and Sidman. Analysis of these sections has begun at Boston, and additional specimens have been provided for sectioning.

Significance to NINDB Program and Biomedical Research: This project represents a unique effort to study human brains from various population groups to determine both gross anatomical variability and microscopic changes through detailed study of the whole brain. There will be considerable archival value to the collection of whole brain sections representing various population groups. In addition, the study of human and chimpanzee brains from Kuru cases will further highlight cellular changes possibly attributable to the disorder.

Proposed Course of Contract: Due to lack of satisfactory pathological back-up at NIH, these studies have been deferred for several years. There exists a considerable backlog of both normal and Kuru brains for processing and analyses. With the head start, experience, and techniques of the Harvard Anatomical Museum group, the study will continue there until this backlog is eliminated, or conclusive evidence of a lack of variability at the structural and cellular levels is gathered.

Serial No. NDB (CF)-65 OAD 1282 (I-XI)
1. Collaborative Field Research
2. Office of Associate Director
3. Bethesda, Maryland

PHS-NIH
Project Report
July 1, 1967 through June 30, 1968

Part A

Project Title: Studies of Child Growth, Development, and Behavior, and Disease Patterns in Primitive Cultures

Sub-Project I: Study of the developmental patterning of the human nervous system (a cybernetics of human development).

1. A research archive for ethnopediatric film investigation of styles in the patterning of the nervous system.

2. Analysis of child care and behavior patterns in primitive cultures from photographic recording (development of techniques and methods.)

3. Investigation of non-recurrent phenomena (objectives and selectivity to be used in documentation of aperiodic phenomena to preserve maximum information.)

4. Analysis of culturally determined methods of approach to symbolic representation from drawings and art forms of children and adults in primitive societies.

Sub-Project II: Human evolutionary study in isolated primitive groups.

1. Kuru.

2. Motor neuron disease and other degenerative diseases in New Guinea and in other inbred Pacific Island populations.

3. Blood group genetic studies in Australasian (Melanesian and Micronesian), and South American indigenes groups.

4. Studies on polymorphism of hemoglobins, red cell enzymes, and serum proteins in Australasian (Melanesian and Micronesian), and South American indegenous groups.

Sub-Project III: Studies of isolated Micronesian populations.

1. Child development and behavior on Ulithi, Ifalik and Lamotrek atolls and Fais Island.

2. Response to live measles virus vaccine in immunological virgin populations without circulating measles virus (with special attention to response in susceptible adults and pregnant women and their offspring).

3. Influenza A2: virgin soil epidemics (epidemiological, clinical, and immunological response and the discovery of populations without previous experience with Type A or Type B influenza.

4. Study of infectious disease patterns in remote individual populations.

5. Genetic characterization of the population of the Caroline Islands.

Sub-Project IV: Studies of isolated New Guinea populations.

1. Child development and behavior in the Western Dani, Asmat, Tjitjak, Auyu, Kayagar groups of West New Guinea, the Kukukuku (Anga) and Eastern Highland peoples of the Territory of Papua and New Guinea, and the Mangsing, Mamusi and West Nakanai of New Britain.

2. Study of infectious disease in the diverse ecologically isolated New Guinea populations.

3. Genetic characterization of New Guinea populations.

4. Hereditary and genetic disease patterns in New Guinea.

5. The Kukukuku peoples: an intensive longitudinal study of child growth, development, and behavior and disease patterns, human genetics and communication in an archaic Highland population of New Guinea.

6. Research cinema films on behavioral patterns of children in New Guinea cultures.

Sub-Project V: Studies in isolated New Hebridean and Solomon Islands populations.

1. Child development and behavior on Tongariki and the Banks and Torres Islands, and with the Ipayato of Espiritu Santo.

2. The Tongariki project: an intensive study of human evolution in the Shepherd Islands.

3. Human genetics and disease patterns survey of the Banks and Torres Islands.

4. Infectious disease seroepidemiology of the New Hebrides.

Sub-Project VI: Studies on Australian aborigines.

1. Arbor virus seroepidemiological studies on Australian aboriginal communities of Cape York.

2. Infectious disease patterns survey of aborigines of Bentnik-Mornington Islands, the Kimberly, the Haast Bluff and Cape York regions of Australia.

Sub-Project VII: Studies on Central and South American Indians.

1. Human genetics and disease pattern studies of the Guayaki and Chaco Indian tribes, and of the Mennonite colonists in the Chaco of Paraguay.

2. Children of the Guayaki Indians of Southeastern Paraguay.

3. Children of the Aroyo (Moro) Indians of Bolivia and Paraguay.

Sub-Project VIII: Developmental, genetic and disease pattern studies in other primitive populations of Asia, Africa and Polynesia.

Sub-Project IX: Experimental developmental neuropediatrics of infantile programming: an empirical approach to the language of information input into the nervous system.
1. Investigation of the social parameters producing "jumpiness"in mice.

Sub-Project X: Ciphers and notation for the coding of sensory data for neurological information processing:
1. Notational systems for human movement.
2. Ciphers and notation for human form, including ciphering for physiognomy, physique, palm printing, ear form and hair.
3. Theoretical study of notational problems in mathematics, linguistics, music, and dance.
4. Alphabet: a theoretical investigation of their relation to linguistics and their application to non-linguistic information.
5. Form recognition: a) neuroanatomic and genetic determination of preferential recognition; b) interrelationships of the problems in computer programming and the arts.

Sub-Project XI: Racial distribution and neuroanatomical variations in the structure of the human brain.

Principal Investigator: D. Carleton Gajdusek, M.D.

Other Investigators: Clarence J. Gibbs, Jr., Michael Alpers, M.D., Barry Adels, M.D., Paul Albrecht, M.D., Edward David, M.D., Paul W. Brown, M.D., Steven Brown, M.D., David Asher, M.D., Vincent Zigas, M.D., Nancy Rogers, Mint Basnight, Lucille Gilbert, Michael K, Nicholson and E. Richard Sorenson.

The Section on Child Growth, Development and Behavior and Disease Patterns in Primitive Cultures has continued all sub-projects listed in the Annual Report of 1966, with expansion of collaborating investigators and institutions which are reflected in the authorship of all publications listed in Part B. The titles of sub-projects and their subdivisions are sufficiently explicit to constitute in themselves the project description.

Part B: Yes

Part A

Project Title: Studies of Child Growth, Development and Behavior, and Disease Patterns in Primitive Cultures.

Sub-Project I: Study of the developmental patterning of the human nervous system (a cybernetics of human development).

1. A research archive for ethnopediatric film investigation of styles in the patterning of the nervous system.

Principal Investigators: D. Carleton Gajdusek, M.D. and E. Richard Sorenson.

Other Investigators: Michael Alpers, M.D., Barry Adels, M.D., Edward David, M.D., Steven Brown, M.D., Vincent Zigas, M.D., Judith Meyer, Peter Fetchko, Donald Rubinstein

Cooperating Investigators: Dr. Paul Ekman, Langley-Porter Neuropsychiatric Institute, San Francisco; William Crocker, Smithsonian Institution; Mathew Stirling, National Geographic Society; Mr. and Mrs. Mark Jablonko, Alan Lomax, Columbia University Department of Anthropology; Dr. Margaret Mead and Dr. T. Schwartz, American Museum of Natural History; Dr. Peter Kundstadter, Department of Anthropology, University of Washington; Thomas Kiefer, Department of Anthropology, University of California; Dr. John Mathews, Public Health Department, Territory of Papua and New Guinea; Dr. Richard Hornabrook, Neurology Department, Wellington Hospital, New Zealand, William H. Bloxam, Department of Territories, New Guinea

Motion picture films and other permanent records are being obtained on a mumber of primtive cultures in collaboration with many outside contributors, and the collection and handling of these are done in accordance with a methodology executed to make these records useful sources of information for future investigators who may not have the opportunity for first hand contact because of the rapidly changing cultures. Our major focus is on child behavior and development, and how these are patterned within a given culture. In collaboration with Langley-Porter Neuropsychiatric Institute in San Francisco and with Columbia University we are developing methods for cross-cultural analysis of nonverbal behavior on a basis of procedure developed the fystematic classification and analysis of non-verbal behavior, which isolated categories of observable movement in each body area measures the duration of the movement and classifies it into an act type on the basis of its distinctive visual appearance. A machine system is in development which can expedite the systematic classification and analysis of non-verbal behavior, and

which has more general utility for application where the human observer must repeatedly view visual information. The hardware for visual information display and retrieval interfaces video tape digitally up to 60 times per second, and allows additional digital information to be written on the video tape, as well as retrieving the visual information by use of the digital data. Our basic question is the extent to which the acts, that is specific movement patterns, differ in their meaning, how they function in different cultural settings. The parallel questions are: how the acts become part of an individual's behavioral repertoire; which acts are programmed neurophysicilogically; which are necessary products of the anatomy and body function; and which are learned as adaptive patterns influenced by the particular ecology, learned in a more imitative sense or through child rearing practices which select certain movements and body functions for the particular emotional displays.

A methodology for preparing Special-category Research Films has been developed to allow research on a restricted area of inquiry unencumbered with the broader material of the Research Films. Such films are assembled as part of research projects which are narrower in scope or different from the purposes for which the original Research Films were made. They, like the Research Films, are assembled in chronological order so as to relate them more easily to their source with its richer peripheral data and not to confuse the time order. Series of Special-category Research Films have been made on Kuru, Nutrition of the Fore, Longlong (an aberrant form of behavior in natives in the New Guinea Highlands) and Indigenous Salt Manufacture of the Kukukuku (Anga) of New Guinea and Motor Neuron Disease in the southwest coast area of New Guinea. The analysis of culturally determined methods of approach to symbolic representation form drawings and art forms of children and adults in the primitive societies is under study.

Part B included: Yes

Serial No. NDB (CF)-62 OAD 969 (I-IV)

1. Collaborative-Field Research
2. Office of Associate Director
3. Bethesda, Maryland

PHS-NIH
Project Report
July 1, 1967 through June 30, 1968

Part A

Project Title: Slow, Latent, and Temperate Virus Infections of the Central Nervous System of Man and Animals

Sub-Project I: Attempts to isolate transmissible agents from sub-acute and chronic diseases of the nervous system

Sub-Project II: Workshop-symposium on slow, latent, and temperate virus infections

Sub-Project III: Fluorescent antibody technique in localizing neurotropic virus antigen in whole animals and cell culture

Sub-Project IV: Studies on the ecology, epidemiology and pathogenesis of arbovirus infections

Principal Investigators: D. Carleton Gajdusek, M.D., and Clarence J. Gibbs, Jr., Ph.D.

Other Investigators: Barry Adels, M.D., Pavel Albrecht, M.D., Michael Alpers, M.D., David M. Asher, M.D., Edward David, M.D., Nancy Rogers, Mint Basnight and J.Hooks

Technical Assistants: Juliette Harvey, Michael Sulima, Helene Gilbert, Edward van Steinberg, Alfred Bacote, Frederick Hess and Herbert Frantz

Student Assistants: Steven Come, Wesley Russell, Robert Rhorer, Judith Christianson and George Bury

Man Years (computed for 12 month period)

Total
Professional:
Other:

The studies reported in this section are being conducted in the NINDB Laboratory of Slow, Latent, and Temperate Virus Infections at the Patuxent Research Center, Laurel, Maryland, in collaboration with the Bureau of Wildlife and Sports Fisheries, U.S. Department of Interior. Additional associated facilities are with the Laboratory of the Study of Child Growth and Development and Disease Patterns in Primitive Cultures, of which this project is a part. (see Project Report Serial No. NDB (CF)-1282 (I-IX.)

Serial No. NDB (CF)-62 OAD 969 (I-IV)
Continued Project 1962 Serial No.
NINDB-CFR-OAD-4

Part A

Project Title: Slow, Latent, and Temperate Virus Infections of the Central Nervous System of Man and Animals

Sub-Project I: Attempts to isolate transmissible agents from subacute and chronic diseases of the nervous system

Principal Investigators: Clarence J. Gibbs, Jr., Ph.D., and D. Carleton Gajdusek, M.D.

Other Investigators: Barry Adels, M.D., Pavel Albrecht, M.D., Michael Alpers, M.D., David M. Asher, M.D., Edward David, M.D., and Nancy Rogers

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of Public Health, Johns Hopkins University Hospital, Baltimore; W. Zeman, M.D., Indiana University Medical Center, Indianapolis; G. ZuRhein, M.D., University of Wisconsin, H. Koprowski, M.D., and M. Katz, M.D., Wistar Institute, Philadelphia; I. Kaye, Department of Neuropathology, University of Vermont; K. Earle, M.D., and P. Lampert, M.D., Department of Neuropathology, AFIP

Technical Assistants: Michael Sulima, Edward van Steinberg, Alfred Bacote, Helene Gilbert, Mint Basnight, and Frederick Hess

Student Assistants and Part-time Temporary Employees: Steven Come, Robert Rhorer, Judith Christianson, and Wesley Russell

Project Description:

Objectives: The objectives of this long-term project remain as established in 1962: 1) to attempt to demonstrate infectious etiology for progressive degenerative diseases of the nervous system of man and animals by transmission to experimental hosts and suitable isolation techniques; 2) to determine the epidemiological significance of established prototype strains of viruses that cause slow, latent, temperate and chronic infections of the nervous system of man and animals; 3) to continue to elicit the biological, physical and chemical characteristics of the prototype strains and newly isolated strains of viruses known to induce slow infections, in order to define the basic biology of the new group of infectious and pathogenic microorganisms; 4) to develop new techniques for the successful isolation, identification, and characterization of the etiological agents of degenerative diseases of the nervous system of man and animals; 5) to develop and modify serological newly isolated agents; 6) to prepare, maintain, establish, and explore cell culture lines of autopsied and biopsied tissues from the central nervous system and other organs of man and animals affected with diseases under study, and to apply these techniques to the study of masking, latency, and temperateness of viruses that cause these slowly progressive degenerative diseases of the nervous system.

Methods Employed: In general, standard and classical techniques for transmission and isolation of viruses are employed with certain notable exceptions; a) the demonstration that the genetic mechanism of the host can determine the host resistance or susceptibility to expression of diseases of interest to our group has required inoculation of specimens into an extensive array of higher primates, i.e., apes and chimpanzees, and a number of species of lower primates, including both old and new world monkeys, as well as domestic animals, i.e., sheep, goats, pigs; and birds--such as ducks, geese, chickens and turkeys--in addition to the entire spectra of ordinary laboratory animals, rabbits, hamsters, guinea pigs, rats, and as many as 17 genetically defined lines of mice; b) a wide variety of tissue and cell cultures from animal and avian sources, as well as explants of tissue from naturally affected man; c) inoculated animals are held in isolation under carefully controlled observation for a minimum of five years in the case of large animals and up to three years in the case of mice and other small short-lived animals; d) pre-bleedings on all animals are tested to deter-

mine base-line antibody spectra, and serial bleedings collected during the course of observation are tested to determine sero-conversion to known agents; in addition, these sera are studied to determine newly formed antigenic properties; e) clinically ill animals are sacrificed with the approval and by recommended procedures of the Animal Care Panel, and serial transmission is attempted by employing the central nervous system and other organs to inoculate the discussed variety of animals; f) detailed neurohistological, as well as general, histological studies are made of each animal that is sacrificed or that has died from nonspecific causes during the study; g) well-established criteria for the selection of cases to be studied, acquisition of central nervous system tissue, preferably at surgical biopsy or at autopsy within a maximum of two hours of death of the patient, and optimal preservation in liquid nitrogen are followed. The following diseases are under study in this laboratory: kuru, Guamanian amyotrophic lateral sclerosis and related Parkinsonism dementia, amyotrophic lateral sclerosis occurring in patients resident in the continental U.S., subacute sclerosing leucoencephalitis, Schilder's disease, Parkinson's disease, multifocal leucoencephalopathy, metachromatic leucoencephalopathy, multiple sclerosis, progressive supranuclear palsy, necrotizing encephalitis. Additional methods being employed in these studies are concerned with that part of the program devoted to laboratory studies designed to more fully define the nature of scrapie virus as a model virus that causes a slow, but progressive, degeneration of the central nervous system of sheep, goats, and mice. Finally, all inocula are tested for the presence of other microorganisms such as bacteria, rickettsia, PPLO, fungi, parasites. During the period covered by this report we have conducted serial studies at programmed intervals on chimpanzees, to determine whether there are any changes in hematology, clinical blood chemistries, cerebrospinal fluid values or patterns of electroencephalograms associated with or preceding the onset of the "kuru syndrome".

Major Findings: Kuru: As reported in last year's annual report, a clinical syndrome, strikingly similar to that of kuru in man, developed in 7 of 8 chimpanzees inoculated in mid-1963 and early 1964 with suspensions of brain tissues from 7 human victims of kuru; the incubation period ranged from 16 to 38 months, mean average 24.5 months, and the course of the clinical illness ranged from 3 to 9 months, mean average 5.5 months. Clinical illness was associated with progressive cerebellar ataxia of the trunk and all limbs and incoordination and wasting lassitude leading to increased disability. There was no gross pathology; histopathological changes were restricted to the central nervous system and consisted of generalized cerebellar system degeneration, marked proliferation and hypertrophy of astrocytes and widespread status spongiosis.

Kuru is the first progressive degenerative disease of the central nervous system of man experimentally transmitted to primates. Thus far, seventy-two chimpanzees have been inoculated with specimens from thirty-seven human kuru victims (42 animals) or from other chimpanzees affected with experimental kuru (30 animals). Among these, twenty-seven have already developed the disease: thirteen after primary inoculation with human tissue, ten on second and four on third passage after inoculation with chimpanzee tissue. Brain tissue from nine human victims has induced disease in twelve animals with incubation periods ranging from 16 to 38 months. In human CNS tissue stored

at -70°C. the kuru virus remains viable for greater than three years. The virus is serially transmissible in primates by intracerebral and peripheral routes of inoculations and can be recovered from visceral tissues as well as brain tissues. Serial passage is associated with a reduced incubation period and the virus is detectable prior to onset of clinical illness. In chimpanzee brain tissue suspensions the virus passes through a 220 mu millipore filter and has an intracerebral infectivity titer in chimpanzees equal to or greater than $10^{-6}/0.2$ ml. Experiments to investigate the possibility of infection on oral inoculation are underway, but chimpanzees fed kuru infected human or chimpanzee tissue have not yet been observed for over 22 months.

Creutzfeldt-Jakob: During the period covered by this report a second human neurological disease, Creutzfeldt-Jakob disease, was successfully transmitted to the chimpanzee. Onset of clinical disease occurred 13 months after inoculation and the course of the disease was 1 month. Additional chimpanzees and a host of other primates and smaller laboratory animals have been inoculated with brain biopsy/autopsy CNS tissues from 8 human victims of Creutzfeldt-Jakob disease. Serial transmission studies and isolation procedures are being conducted on tissues from the first affected chimpanzee.

Subacute Sclerosing Panencephalitis: Employing complement-fixation, hemagglutination-inhibition, neutralization and fluorescent-antibody techniques attempts have been made to elucidate the nature and mechanism of the hyperimmune response to measles virus antigen which we have successfully demonstrated to be a phenomena closely associated with subacute sclerosing panencephalitis disease in children. Attempts are being made to transmit the disease to an experimental host and to isolate a virus from tissues of patients. During this year transmission experiments and isolation attempts have been made utilizing surgical biopsy or early autopsy brain tissues from over 30 patients. Long-term maintenance of successfully explanted cultures of most of these brain tissue specimens is being followed for isolation studies. Over 250 coded paired sera and CSF specimens have been tested against 9 myxovirus antigens. Hyperimmune titers to measles virus antigen were elicited in serum and CSF of only SSPE patients. Studies are being continued in attempts to isolate measles virus from these patients.

Scrapie: Studies to define better the nature of the scrapie virus have been continued and expanded. The most significant findings during the period covered by this report have been: 1) the observation by electron-microscopy of previously undescribed structures ranging from 700-1000 A in 15 of 30 mouse brains infected with scrapie; and, the observation of globular particles ranging up to 1000 A in size in infected mouse brain tissue following purification and concentration of homogenates with fluorocarbon treatment, enzyme digestion and density gradient centrifugation; 2) demonstrated that infectious nucleic acids could not be isolated from scrapie infected mouse brain tissue employing standard techniques; 3) demonstrated scrapie infectivity were partially inactivated by exposure of suspension of infected mouse brain tissue to ultra violet irradiation at energy levels of 4×10^{4} erg/mm^2; 4) demonstrated that mice that had received multiple doses of scrapie-infected mouse brain tissue suspension mixed with Freund's complete adjuvant and exposed to X-irradiation developed clinical scrapie but on histological examination the CNS failed to manifest any morphological characteristics of an antigen-antibody reaction typical for neurotropic mouse agents; 5) using a

modified passive protection-type neutralization test demonstrated in vivo mouse neutralization of scrapie infectivity of >1.0 log. 6) completed phase 1 of the study to prepare crude and sucrose acetone extracted antigens from CNS and visceral tissues of mice sacrificed at 30 day intervals after inoculation with mouse adapted virus. Serological evaluation is in progress. Data have now been collected which suggest that failure to detect humoral antibody in scrapie affected animals may be directly influenced by antigen-antibody complexes formed in vivo. A number of techniques are now being utilized to further demonstrate the complexes, dissociate the bonds and elicit free antibody and free viral antigen. Immunofluorescent studies are reported in Project Serial No. NDB (CF)-63 OAD 1140.

Significance to bio-medical research and the program of the Institute: The successful primary transmission of kuru from humans to a single experimental host, the chimpanzee, and the subsequent successful transmission of kuru from chimpanzee to chimpanzee, particularly with a 220 mu filtrate of infectious chimpanzee brain tissue suspension coupled with the successful retransmission of the disease from one of the human specimens known to induce disease has provided the first significant break through in establishing an infectious etiology for chronic and subacute progressive degenerative diseases of the nervous system of man. The results obtained thus far in this laboratory provide optimism in our attempts to isolate the agent of kuru as well as for multiple sclerosis, amyotrophic lateral sclerosis, subacute sclerosing leucoencephalopathy, etc.

Proposed course of the project: 1) Identification and characterization of the agent causing disease in chimpanzees; 2) continued long term observation of inoculated animals. Continued serial studies on the fractionation of serum specimens from these animals for the determination of shifts in the electrophoretic patterns, as well as their antibody status which may be indicative of sub-clinical infection; 3) continued effort to develop suitable antigen antibody system for the study of established strains of 'slow' viruses; application of these new techniques to the study of human disease; 4) intensification of the development and application of fluorescent antibody techniques with the model virus and other chronic viruses, such as LCM and rabies, which may remain latent for many years before clinically apparent disease becomes manifest; 5) greater emphasis on growth, cultivation and establishment of cell culture lines of "target organ" nervous tissue from human and animals with degenerative diseases of the nervous system, as well as from cases of "auto-immune" diseases in an effort to isolate an etiological agent in a controlled in vitro environment, detection of abnormal antigenic fractions giving indirect evidence of disease and possible association with known viruses and establishment of new cell lines for the study of viral growth, maturation, and measurement of interferon or interferon-like substances; 6) increased efforts to adapt strains of 'slow' viruses to growth, serial propagation and characterization in tissue and cell culture systems; 7) continued efforts toward the development of procedures for the successful isolation of etiological agents responsible for degenerative diseases of the CNS, such procedures to include cell culture blocking techniques, detection of endosymbiotic relationship of masked, latent, or temperate viruses and cells in culture and chemotherapeutic lowering of animal resistance to infection; 8) continued efforts to broaden experimental host range for kuru

and, at the same time, seek out those experimental hosts whose genetic mechanisms render them susceptible to other human diseases under study.

Part B included: Yes

Part A

Project Title: Slow, Latent, and Temperate Virus Infections of the Central Nervous System of Man and Animals

Sub-Project II: Workshop-Symposium on Slow, Latent and Temperate Virus Infections

Principal Investigators: D. Carleton Gajdusek, M.D., and Clarence J. Gibbs, Jr., Ph.D.

Other Investigators: Michael P. Alpers, M.D., and Paul W. Brown, M.D.

Cooperating Investigators: See: List of Participants and Table of Contents in: Slow, Latent and Temperate Virus Infections. Editors: D. Carleton Gajdusek, Clarence J. Gibbs, Jr., and Michael P. Alpers, M.D., National Institutes of Health, 1965. (Monograph of papers presented at the Workshop-Symposium.)

Part B included: Yes

Part B: Publications

Gajdusek, D.C., Gibbs, C.J., Jr., and Alpers, M.P., editors: Slow, Latent and Temperate Virus Infections, NINDB, Monograph No. 2 (PHS publication No. 1378) U.S. Government Printing Office, 1965.
(Monograph on Workshop and Symposium held at the National Institutes of Health, Bethesda, Maryland, December 7-9, 1964; 44 papers, 7 definitive bibliographies, subject index and authors index)

Contributions in above Monograph from this section:

Gajdusek, D.C.: Kuru in New Guinea and the origin of the NINDB study of slow, latent and temperate virus infections of the nervous system of man.

Gibbs, C.J., Jr., and Gajdusek, D.C.: Attempts to demonstrate a transmissible agent in kuru, amyotrophic lateral sclerosis, and other subacute and chronic progressive nervous system degenerations of man.

Alpers, M.P.: Epidemiological changes in kuru, 1957 to 1963.

Gibbs, C.J., Jr., Gajdusek, D.C., and Morris, J.A.: Viral characteristics of the scrapie agent in mice.

Morris, J.A., Gajdusek, D.C., and Gibbs, C.J., Jr.: Spread of scrapie from inoculated to uninoculated mice.

Definitive Bibliographies:

Kuru in New Guinea
Scrapie with References on Rida
Visna
Maedi
Aleutian Mink Disease with References on Chediak-Higashi Syndrome in Mink and Cattle
Chediak-Higashi Syndrome
Hemorrhagic Fevers in South America

Part A

Project Title: Slow, Latent, and Temperate Virus Infections of the Central Nervous System of Man and Animals

Sub-Project IIA: Conference on Measles Virus and Subacute Sclerosing Panencephalitis

Principal Investigators: D. Carleton Gajdusek, M.D., and Clarence J. Gibbs, Jr., Ph.D.

Other Investigators: Michael P. Alpers, M.D., B. Adels, M.D., Nancy Rogers, P. Albrecht, M.D., and J.J. Hooks

Cooperating Investigators: See: List of Participants and Table of Contents in: Conference on Measles Virus and Subacute Sclerosing Panencephalitis (September 13, 1967). Neurology, 18, Part 2 (January) 1968.

Part B included: Yes

Part B: Publications

Adels, B.R., Gajdusek, D.C., Gibbs, C.J., Jr., Albrecht, P., and Rogers, Nancy: Attempts to transmit subacute sclerosing panencephalitis and isolate a measles related agent, with a study of the immune response in patients and experimental animals.

Serial No. NDB (CF)-62 OAD 969 (I-IV)
Continued Project 1963 Serial No.
NDB (CF)-63 OAD 1140

Part A

Project Title: Slow, Latent, and Temperate Virus Infections of the Central Nervous System of Man and Animals

Sub-Project III: Fluorescent antibody technique in localizing neurotropic virus antigen in whole animals and cell cultures

Principal Investigators: Pavel Albrecht, M.D., Clarence J. Gibbs, Jr., Ph.D., Paul Brown, M.D., and D. Carleton Gajdusek, M.D.

Other Investigators: Michael P. Alpers, M.D., Nancy Rogers, Mint Basnight, Charles Plank, M.D. and Jacob Brody, M.D., Epidemiology, NINDB; Kendall Smith, Ph.D., DBS; M.W. Brightman, NIH, Edward David, M.D., Barry Adels, M.D.

Cooperating Investigators: J. Hotchin, M.D., Division of Laboratories, New York Department of Health, Albany; Paul Brown, M.D., Konrad Hsu, Ph.D., Columbia University, New York

Project Description:

Objectives: Use has been made of lymphocytic choreomeningitis virus as a model in establishing the methodology to be used in studies of other central nervous system diseases wherein a suspicion of possible virus etiology is entertained and to define the pathogenesis of LCM. To prepare fluorescent animal anti-sera to antigens in brain tissue of kuru, amyotrophic lateral sclerosis and other chronic central nervous system degenerative disorders; to purify and concentrate scrapie virus and prepare FA reagents in a search for specific antigens in infected tissues. To elicit and more clearly define measles virus as the etiological agent of subacute sclerosing panencephalitis.

Methods Employed: Lymphocytic choreomeningitis and acute neurotropic arboviruses in mice are used as developmental tools in establishing fluorescent antibody techniques in the localization of virus antigen during a slow virus infection involving the central nervous system. Scrapie virus subjected to fluorocarbon deproteinization purification and ultracentrifugation concentration is being studied. A variety of experimental hosts are being immunized with vaccines and serum fractionation procedures are being employed to elicit an immune response.

Major Findings: The demonstration of scrapie antigen fluorescent antibodies using terminal stage sera from diseased mice and sheep in cryostat and paraffin embedded sections has continued to be unsuccessful. These studies are, however, being currently supplemented using hyperimmune sera from animals prepared with different purified fractions.

A factor was detected in certain rabbit and guinea pig sera which shows selective affinity for the hypertrophied astrocyte in scrapie-infected mouse brain sections. Its localization is visualized by staining treated

sections with a fluorescin-conjugated anti-rabbit or anti-guinea pig gamma globulin. Among many kinds of primary hyperimmune sera tested, only rabbits or guinea pigs immunized with whole human brain tissue showed affinity for "scrapie astrocytes". The factor is heat stable, can be removed by absorbing the serum with human brain homogenate or increasing doses of brain from phylogenetically lower mammals.

On the assumption that scrapie may represent a state of immunological unresponsiveness developed perhaps in the course of infection: a) animals were harvested at consecutive time intervals after infection to see whether an immunological conversion from a responsive into an unresponsive, tolerant state develops; b) the antibody-forming system was influenced repeatedly during infection by doses of complete Freund adjuvant followed 24 hours later by X-ray irradiation of a part of the body. Histological examination failed to demonstrate the morphological characteristics of an antigen-antibody reaction typical for neurotropic mice agents. Serological and immunofluorescent evaluation is in progress.

Demonstration of different virus antigens in fixed, paraffin embedded nervous tissue: If tissues carrying a slow neurotropic agent and processed in the usual way by fixation and paraffin embedding are to be examined by the fluorescent antibody technique, information is necessary on the effect of various histological techniques on the preservation of virus antigens. For this purpose 6 arboviruses, herpes simplex virus, rabies virus, LCM, and mumps virus in mouse brain were used. Results obtained so far on viruses of the arbo group show that provided certain precautions in the embedding of the infected brain tissue are observed, the virus antigens can be well localized on a cellular level.

The FA technique was employed to demonstrate specific measles viral antibody in the serum and CSF of humans with subacute sclerosing panencephalitis. The techniques developed in this laboratory proved to be somewhat more sensitive in measuring the levels of antibody to measles. In some instances it was possible to demonstrate specific FA staining of antigen intracellularly in the biopsy specimens of the CNS of human victims.

Significance and Course: Study of LCM as an example of the slow or latent virus infection and, particularly, as an example of the phenomenon of acquired immune tolerance to infection in the mouse. This work on the pathogenesis of lymphocytic choreomeningitis is used both as a valuable addition to our knowledge in its own right and to establish proceedings which may aid in localizing virus antigen.

Proposed Course: Special attention will be directed towards the study of scrapie and kuru agents in experimental animals. Work on other neurotropic viruses, namely, herpes simplex virus, rabies, mumps, LCM, and some arboviruses is intended in a supporting capacity during elaboration of methodological approaches.

Work will continue on purification of virus material to prepare antigens for immunization and serological procedures (agar precipitation, CFR). The immunization procedure will include long and short-term schedules, using live and killed virus preparations in different stages of purification.

Using labeled immune sera the demonstration of antigen-antibody reaction will be attempted in brain and organ sections from infected animals and in sensitive antigen precipitating tests.

With the possibility in mind that scrapie and kuru may represent infections leading to a state of immunological unresponsiveness (tolerance) or that the infectious agent is for practical purposes non-antigenic, appropriate approaches will be devised for the study of interference phenomena, cytotoxic reactions, presence of acquired transplantation antigens, aided where possible by the FA technique.

Reagents are being prepared which will provide for the screening by FA procedures of all long-maintained explant cultures of human and animal tissues to determine the presence or absence of intra or extracellular viral antigens as an aid to isolation and identification of latent, masked or chronic viruses.

Part B included: Yes

Part B: Publications

Albrecht, P.: Pathogenesis of neurotropic arbovirus infections. Current Topics in Microbiology and Immunology, 41 (July) 1968

Adels, B.R., Gajdusek, D.C., Gibbs, C.J., Jr., Albrecht, P., and Rogers, Nancy: Attempts to transmit subacute sclerosing panencephalitis and isolate a measles related agent, with a study of the immune response in patients and experimental animals. Neurology, 18, Part 2 (January) 1968.

Part A

Project Title: Slow, Latent, and Temperate Virus Infections of the Central Nervous System of Man and Animals

Sub-Project IV: Studies on the ecology, epidemiology and pathogenesis of arbovirus infections

1. Epidemic hemorrhagic fevers
2. Seroepidemiology of arbovirus infections in ecologically isolated primitive indigenous populations:
   a) Seroepidemiology of Alaskan populations
   b) Seroepidemiology of the populations of the Caribbean and Central and South American countries with particular reference to Puerto Rico, Bolivia and Paraguay
   c) Seroepidemiology of Australasian populations
3. Japanese B Encephalitis studies on Guam (NDB (CF)-66E1321)
4. Persistence of arbovirus infections

Principal Investigators: Clarence J. Gibbs, Jr., Ph.D., D. Carleton Gajdusek, M.D., David M. Asher, M.D., Jacob Brody, M.D., and Charles Plank, M.D.

Other Investigators: Edward David, M.D.

Cooperating Investigators: K. Shah, M.D. and F. Bang, M.D., Johns Hopkins University School of Public Health, Baltimore; B. K. Aikert, M.D., Institute of Post-Graduate Medical Research, Calcutta; J. Casals, M.D., Yale University, New Haven, J. Brody, M.D., Epidemiology, NINDB, J. Sever, M.D., NINDB; G. Wisseman, M.D. and E. Rosenzweig, Ph.D., University of Maryland, Department of Microbiology; R. Hornabrook, Kuru Research Center, New Guinea; F. Schofield, M.D., Public Health College, Gandar, Ethiopia; P. Allen, Ph.D., V. and R. Division, Ft. Detrick; R. Taylor, M.D., University of California School of Public Health

Project Description:

Objectives and Methods: a) Japanese B encephalitis on Guam: Work has continued into the epidemiology, ecology and antigenic relationships that exist among the arboviruses in an effort to determine their public health importance and prevalence in selected populations. During the period covered by this report studies were continued in collaboration with the Epidemiology Branch of NINDB designed to determine the neurological sequelae in humans that may have suffered inapparent infections during the perinatal period with Japanese B encephalitis on the island of Guam. (See NDB (CF)-66 E 1321 Annual Report July 1, 1966 - June 30, 1967.)

b) Persistence of Arbovirus Infections: Attempts are underway to investigate the mechanisms involved in persistent arbovirus infections of

neural and other tissues. The virus Junin (Tacarike group) produced no chronic illness in surviving mice. (Blind passage experiments are planned.) The group B virus Modoc has only recently been found responsible for a case of encephalitis in a child. One strain of this virus has recently been found to produce persistent asymptomatic infections in hamsters. This virus is less dangerous than Junin, and can be studied by tissue culture and plaque techniques and hemagglutination (as well as by mouse inoculation). We are now preparing reagents (seed pools, hemagglutinating antigen and antiserum) for the study of this virus.

Proposed course of the project: Future plans call for completion of the serological survey and detailed neurological examination by resident neurologists. It is proposed that when the present laboratory investigations are completed, these specimens be examined with antigens of other viruses of the ARBO B group. Also, when clinical examinations of those people with significant titers are completed, some conclusions can be made about the neurological sequelae of sub-clinical Japanese B encephalitis infections.

Part B included: Yes

Part B: Publications

Albrecht, P.: Pathogenesis of neurotropic arbovirus infections. Current Topics in Microbiology and Immunology, 41 (July), 1968.

Pennington, R.J. and Gibbs, C.J., Jr.: A simplified method for preparing Eastern and Western equine encephalomyelitis complement fixing antigens. Proceedings of the Society for Experimental Biology and Medicine, 125, 787-789, 1967.

Part B: Publications

Kakulas, B.A., Lecours, A.-R. and Gajdusek, D.C. Further observations on the pathology of kuru (a study of two cerebra in serial section). Journal of Neuropathology and Experimental Neurology, 26:1 (January), 85-97, 1967.

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Publications (continued):

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Rogers, Nancy G., Basnight, M., Gibbs, C.J., Jr. and Gajdusek, D.C. Latent viruses in chimpanzees with experimental kuru. Nature, 216: 5114 (November 4), 446-449, 1967.

Simmons, R.T., Gajdusek, D.C. and Nicholson, M.K. Blood group genetic variations in inhabitants of West New Guinea. With a map of the villages and linguistic groups of South West New Guinea. American Journal of Physical Anthropology, 27:3 (November), 277-298, 1967.

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ANNUAL REPORT
July 1, 1967 through June 30, 1968
Special Projects Branch—Collaborative and Field Research
National Institute of Neurological Diseases and Blindness
National Institutes of Health

The Special Projects Branch is comprised of two broad-scale collaborative programs, one in head injury and one in epilepsy. Following a period of rapid expansion in FY 1967, these programs maintained their level of activity in FY 1968. Further growth was impossible because budgetary allocations for 1968 were at the 1967 level.

Section on Head Injury

During FY 1967 the Section on Head Injury has attempted to launch collaborative clinical studies of the late effects of head injury, has continued studies of the physical properties of tissues, and has given careful attention to the problems of developing data on the incidence and nature of head injuries in a civilian population. Staff has been augmented with the addition of two physicians—Dr. Alexander Taylor, a visiting scientist from Belfast, Ireland, who is serving as Acting Head of the Section, and Dr. R. Wayne Hurt, who is providing medical support for the development of follow-up studies.

During FY 1968, planning for the 15-year follow-up study of 1200 veterans who had sustained head injuries in the Korean conflict was largely completed. The criteria for selection of control subjects were revised, and the process of locating and contacting control subjects was begun. Interviews of the injured veterans and their relatives and employers have been carried out by the American National Red Cross, Service to Military Families Division. Over 600 interviews have been completed and the schedules have been returned to the Head Injury Section, containing information on work status, occurrence of epileptic seizures and posttraumatic symptoms. This information is being edited as it arrives and forwarded to the National Research Council Follow-up Agency for coding and storing with the information already gathered and coded on original injury and follow-up clinical studies. It has not been possible to proceed to the hospital examination of the veterans due to lack of funds and other factors. A continuous process of revision and improvement of protocols for examination has gone on through consultation between investigators at interested university centers and Head Injury Section staff. Improvements have been made, particularly in methods of studying central auditory and vestibular function, cerebral blood flow, and in the analysis of EEG records. The state of readiness is such that examinations could proceed within a very short time of funding of the further stages of the project.

Current plans, endorsed by the National Advisory Neurological Diseases and Blindness Council Subcommittee on Head Injury, call for conduct of clinical studies at various university medical centers. These independent studies will investigate certain closely delineated facets, such as the onset and cessation of posttraumatic epilepsy, characteristics of the posttraumatic syndrome, current status of neurologic deficit resulting from trauma, and other related studies. Data from these studies would be analyzed separately, but certain

common procedures will be standardized, allowing some pooling of data by the Section for overall analysis. These clinical studies will be initiated as funds become available and interested centers can be encouraged to submit proposals.

The head model construction program, begun in FY 1967, has made considerable progress. The goal of this program is the development of accurate physical and mathematical models of the head which can be used for intensive studies of the characteristics and effects upon the head of various forces of injury. Three institutions have initiated studies of the physical properties of tissue under NINDB research contracts. The first year of these contracts which ends in June, 1968, has been devoted to the preliminary in vitro testing of materials, the development of instrumentation for more complicated in vivo measurements, the development of constitutive equations, and preliminary mathematical studies. Upon completion of the determination of the physical properties of tissues, non-biological materials demonstrating the same properties will be selected, physical models of varying complexity will be developed and various loads will be applied to these models. The entire model construction program will take several years. During the forthcoming fiscal year, the three contractors will continue work on the first phase of the program.

Studies of the incidence and nature of head injury have been temporarily interrupted. A pilot study in the Buffalo, New York, area was initiated by Cornell Aeronautical Laboratory in June, 1967. The first year was devoted to preparing for an in-depth survey: soliciting support of local hospitals and the medical society, planning for a household survey, and developing data processing procedures. In considering questions raised by the Bureau of the Budget, during clearance of the study forms, regarding the practicality of the study, NINDB made a decision to discontinue the project and consider other methodologies for gathering information. Funds are not available to support alternative studies in fiscal years 1968 or 1969.

In addition to these activities, the Section has been engaged in other projects such as the completion of a standardized glossary of head injury terminology and the analysis of data derived from long term follow-up of 1000 German veterans of World War I who sustained combat head injuries.

Section on Epilepsy

All of the activities initiated in FY 1967 have been continued and further developed in FY 1968. The anticonvulsant drug program has enlarged more than any other single activity. The two major staff additions have been Mr. Lawrence D. Smith, a pharmacist, and David J. Goode, M.D.

In the Collaborative Study of Epilepsy, a final total of one hundred and seventy-one (171) patients were admitted to study through April 30, 1968. The collaborating clinical investigators' request that an additional year be given for phase I was turned down by Special Study Section on February 1, 1968. It was recommended that phase I be terminated in an orderly fashion not later than December 31, 1968. Therefore, the last patient was admitted for study

on April 30, 1968. During four quarterly meetings and three EEG workshops, data collection forms were revised, and selected forms were precoded to facilitate card punching. A technique of video recording with joint examination of patients having absence seizures were developed and applied to (a) measure the uniformity of observers and (b) improve consistency and completeness of observations. While improved uniformity of observations was achieved, it was learned that the complete uniformity of detailed description of minute motor accompaniments of absence seizures could not be accomplished without multiple viewing of absence attacks recorded in real time on video tape. The method of data storage was modified to develop a master file program which would facilitate retrieval and afford flexibility for future modifications. The software package for creating, updating, and retrieving the entire data system generated for the Collaborative Study of Epilepsy has been 80 percent completed.

An easily usable EEG check sheet has been developed, coded, stored and computed for meaningful data retrieval. The psychology consultant visited each clinical center and rendered helpful advice concerning not only the present quality and consistency of psychological testing, but also gave a realistic appraisal of future potential of each center for its participation in phase II. The multicamera television system was perfected, and the desired quality of recording is now being consistently maintained at the recording unit at the University of Virginia. Further evidence of a significant delay in skeletal maturation in comparison to the available standard was obtained, and a follow-up study of confirmation was planned.

This Section has developed and maintained liaison with interested pharmaceutical companies to obtain pharmacologic data and information as to the availability of unmarked anticonvulsant drugs for clinical testing. Some eight such drugs are in phase III of clinical investigation. Others are in preclinical status. Two state hospitals have been encouraged to submit proposals for testing anticonvulsant drugs in their epileptic population. One hospital's proposal—New Castle State Hospital, New Castle, Indiana—has been reviewed for technical merit, and a contract was negotiated. The other hospital—Lynchburg Training School and Hospital, Lynchburg, Virginia—is refining its protocol and establishing data on a group of patients suitable for drug evaluation. A Symposium "Laboratory Evaluation of Antiepileptic Drugs" was sponsored by the Institute and administratively supported by the Section on Epilepsy. The Symposium held in Salt Lake City, Utah, May 13-14, 1968, brought together leading investigators in the field from pharmaceutical industry and university laboratories. The aim of the Symposium was to demonstrate new approaches in the area of drug screening to provide new tools for research in development of anticonvulsant drugs by the industry. The proceedings of the Symposium will be published as a single issue of Epilepsia. It is anticipated that the second contract for clinical anticonvulsant drug evaluation program will be negotiated in FY 1969. Such drug studies will provide the industry with population for drug testing not presently available, and will encourage clinical testing on a sound basis. It is to be expected that the result will be earlier determination of efficacy and safety of anticonvulsant drugs so that new and improved agents will become available to epileptic patients. Also anticipated is a preclinical testing of promising

agents under Institute contract as a further stimulus to industry for the development of new agents which might not otherwise receive deserved attention.

In cooperation with the Office of Program Analysis, NINDB, the Section has supervised the initiation of Epilepsy Abstracts, a monthly abstract journal, made available to interested scientists working in related basic and clinical sciences. While the abstracts are selected and compiled by a contractor, the Section supervises the final make-up of each issue in cooperation with the NINDB Information Office, monitors each issue for the quality of selection, preparation of abstracts, classification and indexing. In conjunction with a group of editorial advisors, constructive critical information is complied and forwarded to the contractor. Volume I, No. 1 was published November, 1967; and Volume II will continue, beginning January, 1969. Abstracts for epilepsy literature published between 1948 and 1968 have been compiled and computerized. This retrospective abstract service will be published in two volumes and made available to investigators before the end of calendar year 1968.

In cooperation with the Epidemiology Branch, this Section has participated in the development of a technique to determine the incidence and prevalence of epilepsy with any given population through means of a survey of the population. A questionnaire developed in collaboration with Howard University's Department of Preventive Medicine is being tested in a pilot project. This Section will give support in the form of clinical neurologic examination and supervision of EEG evaluation.

The Section's staff support for the activities of the Public Health Service Advisory Committee on the Epilepsies has been continued and greatly extended to the activities of the Task Force for Basic Research. When the Committee met in September, 1967, they recommended that a scholarly monograph on the basic mechanisms of epilepsies be produced, and that this should be accomplished by bringing together basic scientists whose basic data has been previously not applied, in a workshop to plan a symposium and preparation of the monograph. This Section, in cooperation with the Office of the Associate Director, carried out the staff work for the accomplishment of the workshop which was held in February, and is further performing the staff work for the symposium to be held in November. A monograph will be published in mid-1969. Under planning and support of this Section, Dr. B. Joe Wilder, University of Florida, conducted a survey of clinical neurophysiology as applied to epilepsy, and presented his report to the PHS Advisory Committee on the Epilepsies in February, 1968. The report has been further revised and edited and will appear as NINDB Monograph #8.

CONTRACT NARRATIVE
Special Projects Branch—Section on Head Injury
July 1, 1967—June 30, 1968

UNIVERSITY OF MICHIGAN (PH 43-67-1136)
TECHNOLOGY INC. (PH 43-67-1148)
WEST VIRGINIA UNIVERSITY (PH 43-67-1137)

Title: Determination of the Physical Properties of Tissues

Contractor's Project Director: Dr. Verne G. Roberts (Univ. of Michigan)
Dr. Lawrence S. Higgins (Technology Inc.)
Dr. James McElhaney (West Virginia Univ.)

Current Annual Level: $163,035 (University of Michigan)
$241,000 (Technology Inc.)
$189,000 (West Virginia University)

Objectives: To develop definitive information on the physical properties of the tissues of the head (scalp, skull, dura, brain, fluids). This objective represents Phase I of a program to construct and test accurate physical models of the head. Various physical properties such as bulk modulus, shear strength, tensile strength, compressive strength, etc., are being determined using specimens from human cadavers, autopsies, and biopsies, and similar specimens from the macaca mulatta.

Major Findings: In general, efforts during the first year have been directed toward developing specialized test equipment and modifications to currently available equipment, determining test perameters in terms of loads applied, establishing mechanisms for securing test specimens, establishing standardized specimens, and testing specimens. The University of Michigan group has emphasized tests on human bone and dura from autopsy and monkey brain in vitro and in vivo. The Technology Inc. group has emphasized the development of miniaturized test equipment to use in conducting human in vivo tests, and testing of soft tissues from human autopsy and biopsy and monkey material. The West Virginia University group has emphasized testing of human bone specimens, taken from autopsy and biopsy materials, and monkey bone specimens.

Significance to NINDB Program and Biomedical Research: It is most important to better understand the effect of various forces of injury upon the brain and skull. Little is known about the anatomical results of various forces and the pathways of destructive forces. Destructive testing in animals and neuropathological studies cannot yield definitive information. The goal of this program is the development of suitable and accurate models to which various stresses and loads can be experimentally applied and the effects accurately monitored. From data derived from such experiments, mathematical models can also be developed. An immediate benefit of ongoing Phase I studies is increased knowledge of the physical properties of biological materials of the head, about which little has been known.

Proposed Course of Contracts: The second year of research is beginning at all three contractors. Completion of the studies of the physical properties of tissues (Phase I) is anticipated during the third year. Upon completion of Phase I, work will begin on Phase II, the selection of appropriate non-biological materials whose properties are similar to tissues. Phase III, the development of and application of forces to physical models; and Phase IV, the development of mathematical simulations will follow Phase II.

CONTRACT NARRATIVE
Special Projects Branch—Section on Head Injury
July 1, 1967—June 30, 1968

CORNELL AERONAUTICAL LABORATORY (PH 43-67-1168)

Title: Study of the Incidence and Nature of Head Injury

Contractor's Project Director: Dr. Jaakko H. Kihlberg

Current Annual Level: $317,000 (FY 1967—two years)

Objectives: To develop statistical information on the incidence and nature of head injury in a distinct geographic area. This study was conceived as a pilot study to test the feasibility of a methodology. If it were found practical, attempts to apply it would be made in other geographic areas in an attempt to develop a representative nationwide sample.

Major Findings: The contractor has succeeded in the following tasks to date: (1) development of detailed study plan including data collection procedures; work flows for data collection, coding, storage, and analysis; and development of study forms for data collection; (2) contact with all hospitals in the study area to solicit their cooperation and establish liaison for the survey period; (3) contact with local medical societies to solicit their members' support in providing follow-up medical data; and (4) establishment of a sub-contract with the State University of New York at Buffalo for the conduct of the household survey. Actual survey operations at hospitals or by household interviews have not started.

Significance to NINDB Program and to Biomedical Research: There is an alarming lack of sound epidemiologic data on the incidence and nature of head injuries in a civilian population. This study would have signified the first systematic attempt to gather specific data on head injuries with medical information available to access site of wounding, characteristics of wounds, and acute phase posttraumatic sequellae.

Proposed Course of Contract: This project was terminated by the Director, NINDB, in March, 1968. The reason given was that the program could not afford further costly studies under this methodology, even if it proved feasible; therefore alternative approaches should be sought.

Serial No. NDB (CF) - 68 SP 1324
1. Collaborative & Field Research
2. Special Projects Branch
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Collaborative Study of Epilepsy, Phase I

Collaborating Investigators: William F. Caveness
Fritz E. Dreifuss
J. Kiffin Penry
J. Preston Robb
C. Wesley Watson
Philip T. White

Other Investigators: Pearl D. Fisher
William Weiss
David J. Goode

Cooperating Units: Division of Neurology, University of Virginia Medical School; Montreal Children's Hospital; Division of Neurology, New England Medical Center; Division of Neurology, Marquette University Medical School.

Man Years:

Total:	6-8/12
Professional:	2-4/12
Other:	4-4/12

Project Description:

Phase I of the Collaborative Study of Epilepsy is a pilot project which was initiated July 1, 1966. The main end towards which a study of the problem of epilepsy is directed includes: (1) The identification and evaluation of conditions associated with or developing from the illness. (2) The extent to which the course of the illness could be altered and an evaluation of methods accomplishing this. (3) Investigation of possible etiological factors simply and in association with each other.

The need for a large cohort of patients selected on the basis of rigid standards for whom the manifestation of the disease are currently and reliably recorded is stressed. A collaborative effort was undertaken by four clinical centers, namely: Boston, Charlottesville, Milwaukee, and Montreal. These centers gave the greatest hope of providing an adequate case load for a collaborative study. The coordinating center was established within the Section on Epilepsy, C&FR, NINDB, for Phase I. It was stressed that the objectives of the proposed pilot study differ, in the large, from the long range study of epilepsy. The primary purpose of the full scale study is to

find answers for unsolved problems on epilepsy. The pilot phase is designed to provide and to test means for developing this information. The general aims are to demonstrate that diverse clinical centers can work together in a uniform manner as regards clinical procedures and laboratory examinations, to further develop and thoroughly test a protocol jointly prepared by the clinical directors with the assistance of study design consultants, and to develop a mode of data storage, retrieval, and analysis, utilizing biostatistical guidance and computer techniques.

The specific aims of the pilot study (Phase I) are: (1) To test protocols for practicality and for completeness in providing required medical data. (2) To measure consistency among collaborating institutions in the selection of patients, using specified testing procedures. (3) To measure the reliability of observations, using specified testing procedures. (4) To test the operation of the coordinating center: (a) To determine whether or not the protocol had been followed, and (b) to observe what the record said and to see if this is what the investigators meant. (5) To test the quality control aspects of the uniformity and the processing of study data, i.e., the administration of the data processing and the accuracy with which data are coded, transcribed and stored in the computer. (6) To provide sufficient material to demonstrate procedures for the summarization and statistical evaluation of the project data, so as to enable clinicians to appraise results of the eventual program with a minimum of delay. (7) To develop and test computer programs for the production of summarized information, statistical analysis, and information on quality control.

To achieve these objectives, a segment of the problem of epilepsies, the recurring absence attacks, are studied in selected detail. This type of seizure disorder was chosen because (1) much remains to be learned concerning its etiology, the site of origin within the brain, its relationship to central nervous system maturation, and its therapy. (2) It can be precipitated and observed by simple office procedures (hyperventilation). (3) It occurs with sufficient frequency to permit the accumulation of considerable data. (4) Reasonably objective measurements of its occurrence and its manifestations are available. (5) The withdrawal or modification of medical regimens is less likely to be associated with serious complications than would be true of other seizure forms. As indicated above, the purpose of the pilot study is not primarily to develop medical information, but rather to provide and test the means for developing such information.

Achievements:

One hundred and seventy-one (171) patients have been admitted to study, the last one having been admitted on April 30, 1968. One hundred and seventy patients have been examined in the first month follow-up visit. With the exception of five patients, all have met their scheduled subsequent visits on the fourth, tenth, and sixteenth months after admission to study. (1) Through monitoring the utilization of forms for data collection and their use in joint examinations, the forms were revised twice. Selected forms were pre-coded to facilitate card punching. (2) A

technique of videorecording the joint examination of patients having absence seizures has been developed and applied to (a) measure the uniformity of observers and (b) improve the consistency and completeness of observations. While improved uniformity of observations was achieved, it was learned that complete uniformity of detailed description of the minute motor accompaniments of absence seizures could not be accomplished without multiple viewing of absence attacks recorded in real time on videotape. (3) Considerable data from the initial and first month visits have been compiled to illustrate to the clincial directors procedures for summarization and statistical evaluation. (4) The software package for creating, updating, and retrieving the entire system generated for the Collaborative Study of Epilepsy is 80% completed.

The major findings to date are: (1) The classification recommended by the Committee on Classification of the International League Against Epilepsy for the absence attack under the subcategory "generalized nonconvulsive seizures" was found to be inadequate for describing and categorizing a single seizure explicitly. (2) An unpredicted trend in skeletal age retardation was found among the patients entered int the study which warrants further investigation into skeletal development rates of epileptics. (3) The subjects studied showed a markedly skewed distribution in I.Q. scores with the greater accumulation toward the lower scores. (4) The study patients were largely normal neurologically with speech defects cited as the most common neurological abnormality.

Proposed Course:

The pilot phase of the Collaborative Study of Epilepsy will be completed December 31, 1968. The major findings noted above will be published. Testing of specific hypotheses concerning the efficacy, toxicity, and mechanisms of action of anticonvulsant drugs will be initiated, utilizing some of the data collection forms, computer program, and patients currently under study.

Honors and Awards:

None

Publications:

None

ANNUAL REPORT
JULY 1, 1967 THROUGH JUNE 30, 1968
EPIDEMIOLOGY BRANCH
COLLABORATIVE AND FIELD RESEARCH
NATIONAL INSTITUTE OF NEUROLOGICAL
DISEASES AND BLINDNESS

Introduction

The major areas of activity of the Branch during the period of this report have been:

I. epidemiologic studies of neurologic diseases;

II. laboratory studies of neurologic diseases;

III. the continued and expanded activities on Guam;

IV. genetic studies of neurologic diseases;

V. the expanded activities of the Section on Ophthalmic Field and Developmental Research; and

VI. collaboration, consultation and services rendered to other groups.

The following personnel have joined the Epidemiology Branch: Edward W. Brink, M.D., who transferred to the Branch from the Peace Corps; Frank Reuling, M.D., ophthalmologist; R. Michael Scott, M.D., who had just completed his internship; Martha Harlem, biologist; Minnie Toure, biologist; Ann Harlan, biologist; and Elaine Lewis, R.N. During this time Chris C. Plato and Elizabeth Ryan, R.N. transferred to other areas within the NIH; Portia Holt took a year off to complete her Ph.D. course work at Georgetown University; and David L. Verlee, M.D. completed his tour and left the Branch.

As the result of acquiring increased staff and experience we now are functioning on a broader and more clearly defined basis. The new Deputy Branch Chief adds strength in methodology and application in the study of chronic diseases. The laboratory is now functional with several important observations and publications to its credit. We have had two physicians on Guam this year and organizationally they have operated efficiently in following our important mission on that island. We have established a section which deals with the genetics of neurologic diseases which has become highly productive and offers an important new and continuing program to our Branch. In addition the Section on Ophthalmic Field and Developmental Research functioned semi-autonomously with an active program here and in their newly acquired clinical facility at the Washington Hospital Center.

I. Epidemiologic studies of neurologic diseases

Highlights have been the demonstration of the failure of penicillin to arrest progression of general paresis in a significant proportion of patients; the failure to find typical Guamanian parkinsonism-dementia among demented populations in Washington area hospitals; the high frequency of extrapyramidal signs in demented patients whether on phenothiazines or not; the surprising frequency of impaired vertical conjugate gaze among demented people which was age dependent but not necessarily drug dependent; the failure to demonstrate a correlation between poor mental or motor performance and history of measles before age two; the high correlation between poor learning and "soft" neurologic signs in school children in normal schools; the demonstration that symptoms frequently described as remote effects of cancer on the nervous system occur in the same rates and patterns among individuals with other chronic diseases implying that the cause for these signs was the general health of the patient and not specifically the cancer; the establishing of a registry of patients with astrocytoma to determine the relationship of astrocytoma and toxoplasmosis; the involvement in a broad group of studies involving a population of middle-class Negros in Washington, D.C. and the population laboratory in Washington County,, Maryland in which we hope to determine the effect of variables such as color and social class on birth weight and neurologic diseases including epilepsy and parkinsonism; the designing and field testing of survey forms for detection of epilepsy through nonmedical channels; studies of hemiparkinsonism which seem to indicate that there are two forms of the disease, one of which is apparently helped by surgery; the documentation of a syndrome of spastic paralysis and hyperreflexia among lepers in New Caledonia; and the collection of sera from 100 MS patients and carefully matched controls.

II. Laboratory studies of neurologic diseases

Our studies of lymphocytes have lead to a successful method of freezing peripheral lymphocytes for subsequent regrowth which aids considerably in the logistics of testing in the laboratory and also provides us with a method to bank individual's lymphocytes. In addition we have developed methods for growth of lymphocytes in monolayers which adhere to glass providing a new method for handling these fragile cells. We also disproved a previous publication which claimed that a specific antigen exists in cerebrospinal fluid to which lymphocytes from multiple sclerosis patients are sensitized. We are now ready in the laboratory to study various antigens found in brains of normal individuals and patients with multiple sclerosis, kuru, ALS, PD, etc., and a series of viruses which have been implicated in chronic degenerative neurologic disease and the effect of these products upon peripheral lymphocytes.

III. The continued and expanded activities on Guam

We continue to follow the same large case load of amyotrophic lateral sclerosis and parkinsonism dementia patients on Guam. Noteworthy has been the finding of neurofibrillary changes in a Filipino who died of ALS with no signs of PD. This man lived on Guam for 20 years and was married to a Chamorro woman. In addition we have documented neurofibrillary changes among Chamorros who did not have symptoms of ALS or PD at death. In order to determine whether ALS is more frequent among Statesiders who lived on Guam we are now following 12,000 individuals who resided for at least one year on the island between 1945 and 1955. Extensive genetic and blood grouping studies still fail to indicate any clear method of genetic inheritance. We are following the offspring of the first 100 ALS and 100 PD patients and matched controls. In addition we are following key cases in which both parents were afflicted with either ALS or PD.

Important information on metabolic diseases should be forthcoming through contracts with the University of California, Berkeley, and Harvard University. In our study of Chamorros living in California we have clear evidence that ALS occurs at approximately the same rate as it does on Guam. In one instance an individual had been off the island for 12 years. We also have encountered two patients with questionable PD, one of whom has been off Guam for about 50 years. The findings in these patients are not typical of the disease seen on Guam. We are keeping close tabs on them in hopes of securing autopsies.

In addition on Guam we have completed a survey of hearing defects and acute otitis media. The rate of deafness on Guam is extraordinarily high and is related to infectious middle ear pathology. To our surprise, however, the actual incidence of acute and chronic middle ear infection is low. This could mean that chronic serus otitis is unusually prevalent or that the risk associated with each infection of the ear for producing deafness is unusually high.

We have begun the detailed study of epilepsy on Guam which should provide important information concerning the occurrence of this disease in a tropical area and methodological insights as to how to conduct surveys in different areas.

We have completed surveys of neurologic diseases other than ALS and PD on Guam. Several hereditofamilial diseases were unusually common while the total absence of classical paralysis agitans in this population was a surprising finding.

IV. Genetic studies of neurologic diseases

Activities of the Section on Genetics in Epidemiology during its first year centered in two areas: genetic and clinical studies of movement disorders, particularly dystonia musculorum deformans (DMD); and genetic evaluation of neurologic disorders seen on Guam, particularly amyotrophic lateral sclerosis.

Movement Disorders: Initial evidence gathered by us suggesting DMD exists in at least two hereditary forms has been strengthened. Three hundred eighty individuals in 88 families have now been examined and in 14 with clearly autosomal dominant pattern of inheritance a variable age of onset and clinical course was noted. In contrast, in 32 Jewish families which show only a single generation affected the age of onset and clinical course are more predictable. This ethnic concentration and clinical distinction coupled with segregation analysis suggesting recessive inheritance indicates there is a second disease with dystonia as its main feature which is also genetically determined.

Collaborative efforts with Dr. Mary Bazelon, Assistant Director of the Neurologic Research ward at Children's Hospital, Washington, D.C., are underway to determine the underlying biochemical defect in these two genetic forms of dystonia.

The results of this study will be of immediate and practical use in genetic counseling and may well throw light on the fundamental mechanisms in some other movement disorders. Already Dr. Bazelon has uncovered what is probably a new disorder of intermediary metabolism in a patient with a variant of dystonia.

Another exciting area is the evaluation of intellectual ability in those with the recessive form of dystonia since affected individuals seem brighter than average. A study is now underway with the assistance of the Medical Advisory Section to the Board of Education in New York City to document this association. If true, we would have the first gene which has a positive affect on intelligence. This would add impetus to the quest for the underlying chemical expression of this gene.

Other studies planned include the exploration of the relationship of dystonia to movement disorders such as torticollis and Parkinson's Disease; a comparison of the forms of dystonia we have seen with that occurring in ethnic groups around the world, particularly northern Sweden and Israel; finally a special report stressing the frequency of misdiagnosis of early DMD, labeling it instead a psychiatric illness, and the harm this does to the patient and his family. Evaluation of genetic factors of Guam amyotrophic lateral sclerosis (ALS) are made difficult because of geography and uncertain demography. However, on the basis of segregation analysis of the pedigree data collected by Guamanian practitioners of all bonafide ALS cases the disease is compatible with recessive inheritance. With this in mind the offspring of marriages in which both partners have ALS have been ascertained and 13 of these offsprings are now over age 35. The examination of these 13 revealed two who had probable early ALS and two others who had possible signs suggesting early ALS. More detailed study of all such offspring is underway since if the disease is a simple recessive each would be expected to develop symptoms eventually.

To gain further information about possible genetic or environmental contributions to ALS and parkinsonism-dementia (PD) on Guam another approach was used. A migrant population from Guam was surveyed to see if these diseases occur with the same frequency in those who have left the island. Demographic and medical information was obtained on the 1853 occupants of 370 Guamanian households in California. Two cases of ALS and two probable cases of PD were found indicating the frequency of these two diseases was similar in this migrant group to that on Guam. These results suggest a genetic factor and/or early exposure to an environmental factor is responsible for each disease.

Hearing loss and otitis media on Guam: Several observers have been impressed with the high rate of hearing loss on Guam. Since genetic or environmental factors might be responsible a comprehensive study was undertaken in 1966. A rate of hearing loss among 1500 school children screened was found to be 3 to 4 times that seen in cities of the U.S. and Canada. More than half of those examined who had hearing loss had evidence of otitis media and severe complications such as perforation of the ear drum were commonly seen. When selective service records of 350 Guamanian men were reviewed for ear disorders fully one-third were found with at least mild hearing loss and of the group disqualified on medical grounds one in six had either severe hearing loss and/or perforation of the ear drum, again a much higher figure than seen in the general selective service population. In contrast, a study of morbidity due to otitis media conducted among Guamanian preschool children indicated a very low rate of symptomatic ear infection. These findings suggested that ear infection rather than simple genetic traits associated with deafness account for the bulk of the hearing loss. Perhaps a unique causative agent and/or unusual host response may contribute to this higher rate of infection seen in older children and men. A special microbiologic study along this line is in order and it would seem appropriate as well to initiate a major educational program among the doctors and practitioners as well as in the Guamanian households concerning the magnitude of this potentially preventable disorder.

Other studies: Programs which have recently been initiated include the following: genetic and clinical evaluation of the trait for bilateral acoustic neuroma (which may be simply a variant of neurofibromatosis); the genetics of dizygotic twinning which is thought by some to be a simple recessive trait; genetic studies on families with aniridia and Wilms tumor (since these two conditions may be the product of a single gene which shows varied expression); survey of Micronesia for rare genetic trait since the geographic isolation makes high levels of inbreeding inevitable.

V. The expanded activities of the Section on Ophthalmic Field and Developmental Research

Twin registry for eye examinations: At the beginning of this fiscal year administrative arrangements were completed for procurement of examination facilities for the twin program. Thorough eye examinations, pertinent medical histories, zygosity determinations, and various anthropometric measurements have been completed on over 375 pairs of twins. These preliminary examinations provide an opportunity to:

1. Obtain base-line measurements to identify and enumerate ocular abnormalities among members of the twin registry as an aid in selection of sub-sets for future investigations.

2. Obtain data for direct estimates of heritability. Descriptive data which will be analyzed include anthropometric measurements, patterns of major retinal vessels, iris stromal patterns and ocular dominance.

3. Offer a careful eye examination and exchange of information for the benefit of the twins and thereby encourage their informed interest in participating in proposed detailed investigations.

With satisfactory progress of the general examination phase, we are now developing the first specific study design utilizing the twin population. This will be an evaluation of heritability of the ocular hypertensive response to topically applied glucocorticoid (steroid) eye drops.

During the past year we have completed an agreement with the Division of Direct Health Services, USPHS which will provide the opportunity to undertake twin examinations in cooperation with the USPHS Hospital facilities. We are now in the process of negotiating with the NAS-NRC Twin Register for an agreement to examine twins residing in the Washington, D.C. and Baltimore, Maryland areas. The latter population would be examined at USPHS Hospital, Baltimore, within the framework of our cooperative agreement.

Television ophthalmoscopy: The television ophthalmoscope is of interest to this Section because of its potential value as a population screening device and also because of the need for collaborative effort in its further development. During the past fiscal year support for this instrumentation development became available and we entered into a contract with the Medical Systems Development Laboratory of the Heart Disease Control Program, Bureau of Disease Prevention and Environmental Control to undertake an analysis of the relative merits and project costs of specific applications of television ophthalmoscopy. They are preparing a detailed development plan and will proceed with design and assembly of a compact, reliable instrumentation system for data acquisition. Clinical trials for data acquisition and preliminary programing for automatic processing of the electronic signals will follow.

Tonometry studies: During the past year data obtained in three separate community-wide surveys were further analyzed. In each field study measurements were obtained using a minimum of 3 separate tonometric methods: Schiotz measurements in the supine position and Goldmann measurements in both the sitting and supine positions.

A new analysis compared the identity of persons who were classified as glaucoma suspects by different methods of the examination. Agreement in selecting positive screenees at various critical screening levels from 20 to 25 mm hg was limited. This finding suggests the need for further investigation of the efficiency of tonometric screening for glaucoma.

An analysis was completed on the relationship between intraocular pressure as measured under survey conditions and the time of measurement. A tendency for lowered pressured among persons examined later in the day was found to be statistically significant. This tendency is consistent with our clinical knowledge of diurnal variation, although the present data do not permit discrimination between an age effect and diurnal variation as the cause of lowered pressure. The findings of this study suggest that the time of measurement can influence comparability of tonometry data collected for epidemiologic investigation.

In the community survey at Salt River Reservation, Arizona, tonometry was performed using the Maklakov Tonometer as modified by Posner and Inglima (applanometer) in addition to measurements with the Goldmann and Schiotz instruments. Analysis of these data were completed during the year and showed that distribution of ocular pressure as obtained using the applanometer was in closest agreement with measurements using the Goldmann tonometer in the sitting position. The differences, although small, were statistically significant, and suggest a real difference in the current calibration scales for these two instruments.

Malignant neoplasms of the eye: Pertinent data have been extracted from 1108 death certificates in which the primary cause of death was assigned to Rubric 192 (malignant neoplasms of the eye) during the years 1959 through 1961. During the past year statistical tables were completed based on certificate information classified according to probable histologic diagnosis. The report in preparation will provide the first description of the U.S. mortality experience with specific ocular neoplasms based on the interpretation of death certificate information.

Ophthalmic survey of two defined native groups in South Pacific islands: A report has been prepared on ophthalmic surveys undertaken among the Nasioi on the island of Bouganville in the territory of Papua and New Guinea, and the Kwaio on the island of Malaita in the British Solomon Islands. This study provided insight into the ocular status of people unexposed to Western Civilization. Evaluation of the results of this study, which was undertaken in collaboration with other medical specialists and anthropologists from Harvard University revealed marked differences in the prevalence of disorders common in our society. Such conditions as hypertension and diabetes mellitus were virtually nonexistent.

The ocular survey revealed very little retinal vascular disease even in older subjects, no elevated determinations of intraocular tension, and almost no significant refractive error. In particular, no myopia was found, which raises the question regarding what portion of this type of refractive error might be due to environmental causes (use-abuse theory) and what contribution is made by heredity as influenced by natural selection. We propose to study this question in conjunction with our examinations on twins.

Influence of synthetically derived aglycone of cycasin on ocular tissue: This study has been continued in collaboration with the Laboratory of Experimental Pathology, NIAMD. Intracameral injections of rabbits using known oncogenic agent (hydroxyazoxymethane) have been completed and the appearance of the ocular fundus has been followed. There has been no evidence of neoplasia or other progressive intraocular change. The period of observation will be continued.

Strabismus study: This study has been undertaken in collaboration with the Biometrics Branch, C&FR, NINDB. They are the principal investigators and will report on this study.

Relationship between acute iridocyclytis and serologic evidence of viral infection: The cause of iridocyclytis remains an enigma. A pilot study to examine the relationship between acute iridocyclytis and serologic evidence of previous or co-existing viral infection is being implemented. Out-patient eye clinics in nearby hospitals will provide a source of patients with iridocyclytis who will be matched with comparison subjects on the basis of age, race, sex, and area of residence. Laboratory of the Section on Viral Diseases, PRB, NINDB, will collaborate in performing complement fixation tests for a series of 40 viral antibodies. Antibody response among the case and control group will be compared for blood specimens obtained at the time of diagnosis and four weeks following diagnosis.

VI. Collaboration, consultation and services rendered to other groups

See following Contract Reports.

CONTRACT NARRATIVE
Epidemiology Branch, C&FR, NINDB
Fiscal Year 1968

THE NATIONAL ACADEMY OF SCIENCES (PH43-64-44)

Title: The Epidemiology of Stroke

Contractor's Project Director: Dean M. Nefzger
Roy Acheson, M.D.
Albert Heyman, M.D.

Current Annual Level: $61,000.00

Objectives: The contractor will: (a) Analyze death certificates of all veterans dying in 1967 in Georgia (high mortality area) and five Rocky Mountain States (low mortality area). From the certificates approximately 1,000 certified CVA deaths in each area and 100 randomly selected controls will be chosen for further analysis (2,200 cases total). From these basic data, the frequency of reported CVA among veterans will be compared with male populations in similar areas to determine if the geographic variations reported for civilians occur among veterans; (b) By review of available hospital records and when necessary by physician or family interview, the validity of the diagnosis will be established in order to estimate the relative frequency of mistaken diagnosis or failure to make the diagnosis of CVA; (c) By review of the accumulated information on veterans dying of CVA an estimate of the relative frequency of specific types of CVA will be compiled; (d) All verified stroke deaths and all errors in death certification will be analyzed in terms of geography, age, race, place of residence, marital status, from the point of view of sources of information (competance of certifying individual) and other variables; (e) During this investigation the complete Military and Veterans Administration folders will be reviewed for a subgroup of 50 cases and controls per state in order to evaluate the usefulness of these records in subsequent studies. In addition, all other avenues of ascertainment of a valid rate of CVA among veterans will be explored in order that a definitive study of veterans population be conducted in the future when the great bulk of veterans of the Second World War arrive at the age of high risk for CVA.

Major Findings: The work to date has indicated that the various sources within the Veterans Administration are available and of sufficient quantity to give important information concerning stroke in male veterans in different geographic areas.

Significance to NINDB Program and Biomedical Research: The epidemiological patterns of stroke are poorly understood although it is suspected that there are regional differences throughout the U.S. Any information confirming these differences and indicating a cause for these differences could lead to a better understanding of causation and prevention in this important cause or morbidity and mortality.

Proposed Course of Project: The project has been extended for another year with the intention of subsequent extension for at least one more year.

CONTRACT NARRATIVE
Epidemiology Branch, C&FR, NINDB
Fiscal Year 1968

THE JOHNS HOPKINS UNIVERSITY (PH43-66-920)

Title: The Epidemiology of Stroke

Contractor's Project Director: Abraham M. Lilienfeld, M.D.

Current Annual Level: $248,203.00

Objectives: The contractor will: (a) Select nine communities (three reporting high incidence, three reporting average incidence and three reporting low incidence), from which data for the national study is to be gathered; (b) develop survey techniques for the examination of death certificates (cerebrovascular deaths and controls), review of hospital records, and physician and household interviews; (c) conduct surveys in the selected communities and validate all or an adequate sample of current cerebrovascular death certificates (CVD as cause or contributing cause of death) and certain controls by review of hospital records and physician interview; (d) analyze these data and, if the sample reveals differences in incidence between communities, techniques will be developed for descriptors of these differences (type of pathology, sex, age, race, etc.).

Major Findings: The major finding of the contract was that differences in mortality in various regions of the country are real and not artifacts.

Significance to NINDB Program and Biomedical Research: Cerebrovascular accidents comprise a major cause of dibility and death. It is only through painstaking and difficult studies such as this that a true indication of the patterns of stroke throughout the country will be possible. It is necessary to have a better understanding in order to design prospective studies to test hypotheses which to date are lacking.

Proposed Course of Project: The project terminated in December 1967. A proposal for a morbidity study in these nine areas was submitted. This was a logical next step in determining if the regional differences in mortality are a reflection of the morbidity in the community or the medical care. The project has not been funded but attempts to extend the mortality information in several of the areas are still underway.

CONTRACT NARRATIVE
Epidemiology Branch, C&FR, NINDB
Fiscal Year 1968

THE JOHNS HOPKINS UNIVERSITY (PH43-67-1347)

Title: The Epidemiology of Parkinson's Disease

Contractor's Project Director: Abraham M. Lilienfeld, M.D.
Irving I. Kessler, M.D.

Current Annual Level: $54,324.00

Objectives: The contractor will: (a) Select a group of hospitals to provide sufficiently large groups of patients with Parkinson's disease; (b) Assemble groups of patients with parkinsonism, Parkinson's disease and similar neurological deficits who have been hospitalized for any reason or seen in any hospital clinic; (c) Assemble matching groups of patients without parkinsonism symptoms who have been hospitalized at the same institutions and who are similar to the cases in age, sex, race, and other pertinent demographic characteristics; (d) Select a probability sample of physicians (neurologists, general practitioners, general surgeons, and internal medicine practitioners) and from them secure a cohort of patients with parkinsonian symptoms who have not been hospitalized; (e) Compare the patients and their matched controls with regard to epidemiologic characteristics of possible relevance to the incidence of or morbidity from Parkinson's disease, including familial mortality experience and smoking histories; (f) compare, within the patient groups, the epidemiologic characteristics of those with specific parkinsonian symptom complexes; (g) Compare the hospitalized and nonhospitalized parkinsonian patients in order to test whether there are methodologic biases in studies restricted to hospitalized patients; (h) Assemble a large group of patients known to have had Parkinson's disease, parkinsonism or similar neurological deficits as the basis for an analysis of the overall and cause specific mortality of the decedents; (i) Reach conclusions as to the adaptability of the case-control method to the study of Parkinson's disease; and (j) To the extent that the case-control method proves to be inadequate, design other more suitable methods for the epidemiological study of Parkinson's disease.

Major Findings: During the time from the awarding of the contract to the present writing the study has been concerned with accumulation of patient and control data. No analysis has been attempted as yet.

Significance to NINDB Program and Biomedical Research: At present understanding of risk factors and natural history in parkinsonism is limited to a few studies primarily in clinic populations. The extension using a case-control matching could provide important information for this extremely important neurologic condition.

Proposed Course of Project: The project will run for two years. At present, however, the first year accumulation of work demands that additional time be devoted to tabulating and documenting the cases and controls. Therefore, the first year of the project was extended until September 1968 without additional funds. At that time the second year of the project will commence should funds be available.

CONTRACT NARRATIVE
Epidemiology Branch, C&FR, NINDB
Fiscal Year 1968

THE UNIVERSITY OF CALIFORNIA-BERKELEY (PH43-68-36)

Title: Health Survey of Stateside Guamanians

Contractor's Project Director: Reuel Stallones, M.D.
Dwayne M. Reed, M.D.

Current Annual Level: $128,378.00

Objectives: The contractor will: (a) Analyze mortality experience of Guamanian residents in California for the past ten years in comparison of that of California residents generally; (b) Contact adult Guamanians residing in California and enlist the voluntary participation in the survey of approximately 1,000 subjects; (c) Secure family and individual health histories from recruited subjects, and administer a screening examination comprised of: neurologic examination, psychological examination to test for dementia and motivational aspects, EKG, BP, blood tests for cholesterol, triglycerides, uric acid, and glucose; (d) Conduct similar examinations of a matched group of Guamanians residing on Rota Island, Saipan Island, and Guam; (e) Code and process data gathered and analyze results, demonstrating whether or not disease patterns vary between Guamanian residents in the U.S. and the general population, and between Guamanian residents in the U.S. and Guamanian residents in the Pacific.

Major findings: The phase of study on Guam is not yet completed; hence there are no comparative findings.

Significance to NINDB Program and Biomedical Research: Establishing a baseline on Guam for metabolic disease and cardiovascular disease as well as some knowledge of psychological patterns and patterns of neurological disease will be invaluable to our studies on Guam. They will also provide important information concerning patterns of disease among migrating populations.

Proposed Course of Project: The project will run for one more year at which time the results will be analyzed and the necessity for further studies will be determined.

Serial No. NDB (CF) - 55 E 201
1. Collaborative & Field Research
2. Epidemiology Branch
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Studies on amyotrophic lateral sclerosis/parkinsonism-dementia complex of Guam (ALS-PD)

Previous Serial Number: Same

Principal Investigators: Jacob A. Brody, M.D.
Thomas E. Henson, M.D.
NINDB Research Center
Edward W. Brink, M.D.
NINDB Research Center

Other Investigators: Jose Torres
NINDB Research Center
Francisco Leon Guerrero
NINDB Research Center
Manuel T. Cruz
NINDB Research Center
Nancy J. Wetmore, R.N.
NINDB Research Center
Joyce M. Cannon, R.N.
Roswell Eldridge, M.D.

Cooperating Units: NINDB Research Center, Agana, Guam
Special Chronic Disease Studies, C&FR, NINDB
Laboratory of Slow, Latent, and Temporate Viruses, C&FR, NINDB
Department of Epidemiology, School of Public Health University of California, Berkeley
Mayo Clinic, Rochester, Minnesota
Department of Pathology, Massachusetts General Hospital Boston
Amino Acid Laboratory, Massachusetts General Hospital Boston
Department of Neurology, Wakayama Medical College, Wakayama, Japan
Trust Territory Health Office
University of California, Los Angeles
School of Public Health, University of Hawaii, Honolulu
Social Security Administration, DHEW

Man Years:

Total:	1
Professional:	3/4
Other:	1/4

Project Description:

Objectives: To determine the cause of ALS and PD and to determine the epidemiological, clinical, neuropathological, and physiological significance of these diseases.

Methods employed: Routine methods for epidemiological, clinical, and neuropathological investigations.

Major findings: During the year 7 patients with ALS; 9 with PD; 4 with PD plus some motor neuron signs; 1 with extrapyramidal signs alone and 2 suspects died. At present we are following 44 patients with ALS; 27 with PD; 2 with PD and motor neuron changes and 3 with extrapyramidal symptoms only. In addition we are following 12 ALS suspects and 12 PD suspects. Of significance was the fact that 1 Filipino who had lived on Guam for 20 years and died of classical ALS had some findings of neurofibrillary changes at autopsy. In addition neurofibrillary changes are being found among Chamorros who did not die of ALS or PD in a study in collaboration with E. P. Richardson, M.D. in the Department of Neuropathology, Massachusetts General Hospital. In the California study of Chamorros with ALS and PD we know of 2 definite ALS patients which is the same rate as found on Guam and 2 atypical suspect PD patients. One of these PD patients had been away from Guam for approximately 50 years.

Brain material from Guam ALS and PD patients inoculated into chimpanzees three years ago is still not producing any symptoms in these or any other laboratory animals.

Offspring of the first 100 ALS patients and the first 100 PD patients who died in the NINDB series on Guam have been matched with offspring of other Chamorros who died in the same years as our patients and who were approximately the same age. Analysis of these data are underway and fail to reveal impressive differences in these groups. In addition key families in which both parents suffered from ALS or PD are being followed.

We have established a registry of about 10,000 statesiders who lived on Guam for more than 1 year and through a contract with the Social Security Administration we are following these people to determine their rate of ALS and PD.

Two approaches to metabolic diseases and their relationship to the neurologic diseases are underway. Both are being developed through contracts: one with the Amino Acid Laboratory, Massachusetts

General Hospital and the other with the University of California, Berkeley.

As the result of our trips to Saipan and Truk we will soon receive material from the census of the Trust Territories which includes all deaths within the past year. It is hoped that from these data we will get some insight as to whether ALS or PD occur at unusually high rates in other islands in Micronesia.

Significance to biomedical research and the program of the Institute: In Guam we have perhaps the highest incidence in the world of motor neuron disease and of a primary CNS degeneration. The documentation of the epidemiological, clinical, and neuropathological aspects of ALS and PD, a major neuromuscular disease and an important primary CNS degeneration have added to the world's knowledge concerning these neurologic diseases. In fields in which there are no known causes and no known cures, data such as these provide one of the most likely avenues for development of concepts and facts which lead to causes and cures.

Proposed course: The epidemiologic studies will continue with and persist on changing patterns in Guam as well as the new studies above. More attention will be given to true understanding of PD and of the real incidence of this disease both clinically and as a neuropathologic entity on Guam. Studies of metabolic disorders and inborn errors of metabolism continue under contracts. We will also have to develop field tools for psychological and neurological screening which will enable us to get a better grasp of the actual manifestation of this disease.

Honors and Awards: None

Publications: Brody, J.A. and Chen, K.M.: Changing Epidemiological patterns of amyotrophic lateral sclerosis and parkinsonism-dementia on Guam. Presented at: Symposium on ALS and Related Disorders, San Francisco, California, 1967.

Brody, J.A. and Chen, K.M.: Recent studies of amyotrophic lateral sclerosis and parkinsonism-dementia on Guam. Presented at: Second Asian and Oceanian Neurological Congress, Melbourne, Australia, 1967.

Chen, K.M., Abrams, B.M., and Brody, J.A.: Serial EEGs of patients with parkinsonism-dementia syndrome of Guam. The EEG Journal (in press).

Serial No. NDB (CF) - 63 E 1103
1. Collaborative & Field Research
2. Epidemiology Branch
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Neurological diseases other than ALS/PD on Guam

Previous Serial Number: Same

Principal Investigator: Kwang-ming Chen, M.D.
NINDB Research Center

Other Investigators: Jacob A. Brody, M.D.
Leonard T. Kurland, M.D.
Mayo Clinic

Cooperating Units: NINDB Research Center, Agana, Guam
Mayo Clinic, Rochester, Minnesota

Man Years

Total:	1/4
Professional:	3/16
Other:	1/16

Project Description:

Objectives: A survey in 1954 by Donald W. Mulder, M.D. and Leonard T. Kurland, M.D. gave the impression that not only ALS but also other heredo-familial neurologic disorders seemed unusually prevalent while multiple sclerosis and perhaps CNS tumors are uncommon. The objective of this study is to try to determine the validity of this data.

Methods employed: Since the establishment of this Center in 1956, we have occupied a unique position on Guam. It is the only neurological consultation service available to all ethnic groups on Guam and sees most neurological patients at Guam Memorial Hospital and Naval Hospital. Therefore, it is expected that most of the significant neurological cases are eventually brought to our attention. By this unique position we hope to determine the frequency of various heredo-familial neurological disorders on the island.

Major findings: Up to April 1, 1967, a total of 1,238 documented cases have been seen by this Center since 1956. Among them are 962 Guamanians, 150 Caucasians, 88 Filipinos and 38 from other ethnic groups. Analyses of these Guamanian cases are presently undergoing review and a detailed report will be available soon. We are impressed that there seems to be an unusual

incidence of certain heredo-familial neurologic diseases on Guam. Examples of this are: five distinct families with 32 myotonic dystrophies; two families with 11 cases of Charcot-Marie-Tooth disease and five sporadic perenial muscular atrophies; a family with four brain tumors, one leukemia among 14 sibs and primary hepatomas in paternal and maternal graddfathers; a family with five cases of narcolepsy; two families with four cases of phakomatosis; a family with three cases of progressive spastic paraplegias; a family with two sibs with hereditary ataxia reminiscent of spinocerebellar degeneration; three families with albinos; six mongols; a family of hypertelorism, etc. No patients with classical paralysis agitans have been observed among Chamorros.

Significance to biomedical research and the program of the Institute: This study adds to the general body of knowledge being collected by the Branch regarding the island of Guam.

Proposed course: A paper on this subject is in preparation. We are also continuing to collect data on Guam.

Honors and Awards: None

Publications: None

Serial No. NDB (CF) - 66 E 1254
1. Collaborative & Field Research
2. Epidemiology Branch
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Comparison of ocular characteristics among monozygous and dizygous twins

Previous Serial Number: Same

Principal Investigator: J. Theodore Schwartz, M.D.

Other Investigators: Frank H. Reuling, Jr., M.D.
Richard E. Goldberg, M.D.

Cooperating Units: None

Man Years:

Total:	5/12
Professional:	1/6
Other:	3/12

Project Description:

Objectives: To develop a local register of twins as a resource for ophthalmic investigations on the heritibility of ocular characteristics, and to undertake case-control studies and studies of the early natural history of chronic disorders.

Methods employed: This Section has compiled a registry of over 500 pairs of monozygous and dizygous twins who will be available for ophthalmic examination. The twin population is being interviewed and given a general eye examination. Blood type, fingerprints and ocular photographs are being obtained. On the basis of information developed through the first examination, subsets of the twin population are to be invited to participate in specific investigations.

Major findings: Ocular abnormalities found among the twin population are being compiled. A series of twins with normal visual acuity and negative history for eye disease has now been compiled for selection of twins to participate in a study of the inheritance of the hypertensive reaction to topically instilled corticosteroid (steroid) eye drops.

Significance to biomedical research and the program of the Institute: If inheritance is found to play a major role in the transmission of the steroid response, this research would offer strong support for the need of further studies to define thoroughly the relationship between steroid

responsiveness and chronic simple glaucoma. If inheritance is found not to play a significant role, the evidence would suggest the need to re-examine a popular hypothesis suggesting simple autosomal transmission of the hypertensive response to steroids.

Proposed course: Additional investigations will be carried out on selected pairs of twins. Early studies will investigate parameters of ocular motility, including a study of heterophoria, ACA ratio, vergence amplitudes and accommodation amplitudes. A prospective investigation on the influence of various treatments on the progress of myopia will be undertaken.

Honors and Awards: None

Publications: None

Serial No. NDB(CF) - 64 E 1257
1. Collaborative & Field Research
2. Epidemiology Branch
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: A study of mortality in the U.S. from malignant neoplasms of the eye

Previous Serial No.: Same

Principal Investigator: David L. VerLee, M.D.

Other Investigators: J. Theodore Schwartz, M.D.
Irving D. Goldberg, Ph.D.
National Institute of Mental Health
Allen R. Lewis, M.S.
Biometrics Branch, C&FR, NINDB
Gail R. Williams, M.D.
Ypsilanti State Hospital

Cooperating Units: Office of Program Planning and Evaluation, NIMH
Biometrics Branch, C&FR, NINDB
Ypsilanti State Hospital, Michigan

Man Years:

Total:	1/4
Professional:	1/8
Other:	1/8

Project Description:

Objectives: To study the U.S. mortality experience with malignant tumors of the eye.

Methods employed Under the present system of classifying causes of death, all fatalities due to malignant neoplasms of the eye or optic nerve are assigned without subclassification to Rubric 192. Retrospective characterization of eye tumor mortality by histologic type requires, therefore, an examination of individual death certificates.

In the U.S. during the period 1959 to 1961, there were 1,108 certificates in which the primary cause of death was assigned to Rubric 192. A full copy of the microfilm image of these death records has been provided by the Division of Vital Statistics, National Center for Health Statistics, on 1,024 certificates. The data from these records has been recorded in a standard format and is now being analyzed. Additional information necessary to classify the diagnosis listed on the death

certificate has been solicited from hospitals and records and the certifying physician in certain cases.

Major findings: Compilation of the data have now been completed and final statistical tables are now available. Estimated annual mortality rate in the U.S. for malignant melanoma is 1.173 per million, for retinoblastoma 0.247 per million and for glioma of the optic nerve 0.047 per million.

Significance to biomedical research and the program of the Institute: Certain epidemiologic features of eye tumor mortality in the U.S. such as age, race, sex, and state of residence are being obtained from this analysis and prepared for publication.

Proposed course: This project is continuing.

Honors and Awards: None

Publications: None

Serial No. NDB (CF) - 66 E 1313
1. Collaborative & Field Research
2. Epidemiology Branch
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Ophthalmic survey of population groups of South Pacific Islands

Previous Serial No.: Same

Principal Investigator: David L. VerLee, M.D.

Other Investigators: J. Theodore Schwartz, M.D.
Robert E. Markush, M.D.
Albert Damon, M.D.
Harvard University

Cooperating Unit: Department of Anthropology, Harvard University

Man Years:

Total:	1/4
Professional:	1/8
Other:	1/8

Project Description:

Objectives: To describe the ocular status of populations residing on two South Pacific Islands.

Methods employed: This Section was invited to join a survey team of medical specialists and anthropologists in the South Pacific to examine the Nasioi on the island of Bouganville in the Territory of Papua and New Guinea, and the Kwaio on the island of Malaita in the British Solomon Islands. Members of the Department of Anthropology, Harvard, had recently completed approximately two years of anthropologic study of these populations, and that Department followed this with medical and epidemiologic investigations. These investigations included general medical evaluation, evaluations in internal medicine, cardiology, pediatrics, dentistry, ophthalmology, general metabolic status, and anthropometry.

Major findings: Among the observations made were the following which are of particular interest because they differ from available data on Western populations.

1. Approximately 95% of all persons had visual acuity of 20/20 or better in the better of the two eyes.
2. Refractive errors, in particular myopia and astigmatism, were rare. Only 10 of the 1155 (0.8%) eyes were myopic, and the myopia in all 10 was

0.5 diopter or less. Astigmatism of 0.75 diopters or more was found in only 61 (5.3%) of the eyes.

3. Schiotz tonometry determinations revealed only three of 812 eyes to have intraocular pressure over 21 mm hg., the pressure in all three was 22.4 mm hg.

4. Arteriosclerotic and hypertensive retinopathy were virtually absent in all age groups.

Significance to biomedical research and the program of the Institute: While no unusual prevalence of any disease process was encountered in these populations, the apparent dissimilarities from Western populations pose interesting opportunities for further epidemiologic investigation. The presence of active trachoma among all examinees from islands neighboring an essentially trachoma-free island may warrent further investigation.

Proposed course: The presence of arcus senilus among the study population and data obtained on determinations of blood cholesterol will be analyzed.

Honors and Awards: None

Publications: VerLee, D.L.: Ophthalmic Survey in the Solomon Islands. Amer J Ophthal (in press).

Serial No. NDB (CF) - 66 E 1314
1. Collaborative & Field Research
2. Epidemiology Branch
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Influence of synthetically derived aglycone of cycasin and methycholanthrene on ocular tissues

Previous Serial No.: Same

Other Investigator: Richard E. Goldberg, M.D.

Other Investigators: Frank H. Reuling, Jr., M.D.
J. Theodore Schwartz, M.D.
Gert L. Laqueur, M.D.
Experimental Pathology Branch, NIAMD
David W. Smith, M.D.
Experimental Pathology Branch, NIAMD

Cooperating Unit: Experimental Pathology Branch, NIAMD

Man Years:

Total:	1/4
Professional:	1/4
Other:	0

Project Description:

Objectives: To study the influence of synthetically derived aglycone of cycasin and methycholanthrene on ocular tissues.

Methods employed: Investigators at NIAMD have shown that the aglycone of cycasin (hydroxyazoxymethane) and other derivatives of the cycad nut can produce hepatic, renal, gastric, pulmonary and cerebral tumors in certain experimental animals. Methylcholanthrene is known to be capable of producing intraocular tumors in the rat.

Techniques of intracameral injection and implantation have been developed and a rabbit population has been exposed to the above agents.

Major findings: Aglycone of cycasin: 33 infected rabbits developed a vasculitis of the retinal vessels which when graded as to severity appears to correlate with dosage. No tumors have been noted to date.

Methylcholanthrene: 12 rabbits given intravitreal injection of methylcholanthrene and observed for a period of nine months failed to demonstrate a clinical response to this drug.

Significance to biomedical research and the program of the Institute: To date this experiment has been negative for tumor formation. A positive outcome would provide evidence for oncogenic capability of hydroxyazoxymethane in "sterile" tissues. It would also provide a laboratory model for experimentation in intraocular tissues.

Proposed course Twelve rabbits selected on the basis of total injected dosage and total observation time are being followed for tumor formation. Twenty-one rabbits have been sacrificed and pertinent tissues have been retained for pathologic studies.

Honors and Awards: None

Publications: None

Serial No. NDB (CF) - 66 E 1315
1. Collaborative & Field Research
2. Epidemiology Branch
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30 1968

Project Title: Tonometry survey among American Indian population, Salt River Reservation, Arizona

Principal Investigator: J. Theodore Schwartz, M.D.

Other Investigators: Douglas K. Powers, M.D.
Division of Indian Health, USPHS
Geoffrey G. Dell'Osso
Biometrics Branch, NINDB
Gail R. Williams, M.D.

Cooperating Units: Division of Indian Health, USPHS
Biometrics Branch, C&FR, NINDB
Institute for Glaucoma Research, New York

Man Years:

Total:	1/8
Professional:	1/16
Other:	1/16

Project Description:

Objectives: The primary objective of this reservation-wide tonometry survey was to obtain, under field survey conditions, a comparison of the performance of Schiotz, Goldmann and a modified Maklakov tonometer (applanometer).

Methods employed: The field investigation was undertaken as a 2-1/2 week mass screening program. Examination facilities were established at two different sites on the reservation. Data were collected on approximately 435 examinees of age 25 and over.

Major findings: During the past year the statistical analysis and report on this investigation was completed. The cumulative frequency distributions of ocular pressure obtained using the Maklakov tonometer as modified by Posner and Inglima (applanometer) were compared with distributions using the Goldmann and Schiotz instruments. Analysis of these data showed that distribution of ocular pressure using the applanometer was in closest agreement with measurements obtained using the Goldmann tonometer in the sitting position. The differences, although samll, were statistically significant, and suggest a real difference in the current calibration scale of these two instruments.

Significance to biomedical research and the program of the Institute: This investigation showed that calibration scales for the tonometers under study are not uniform. Consideration must be given to such variation when attempts are made to collect data for purposes of epidemiologic comparison.

Proposed course: This project is completed.

Honors and Awards: None

Publications: Schwartz, J.T., Dell'Osso, G.G., and Powers, D.K.: Compairson of Modified Maklakov (Posner-Inglima) Goldmann and Schiotz Tonometry. In: Monograph on Applanation Tonometry, A. Posner, Ed. (in press).

Serial No. NDB (CF) - 66 E 1319
1. Collaborative & Field Research
2. Epidemiology Branch
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Determining autoimmunity in chronic neurological diseases by the use of peripheral lymphocytes

Previous Serial Number: Same

Principal Investigator: Jacob A. Brody, M.D.

Other Investigators: Charles R. Plank, M.D.
Martha M. Harlem
Minnie Toure

Man Years

Total:	1/4
Professional:	1/12
Other:	3/12

Project Description:

Objectives: Our immediate objective is to develop a quantitative method to measure the transformation reaction of lymphocytes in vitro. We then intend to survey chronic neurological diseases by this method to discover possible immune mechanisms such as delayed hypersensitivity or autoimmune phenomena.

Methods employed: The basic methods employed have not changed during the year. New techniques have been developed which are discussed under "Major Findings."

Major findings: We have developed a technique for freeze-thawing of lymphocytes and in addition for the culture of lymphocytes in monolayers by coating petri dishes and cover slips with 0.5% gelatin. We completed the study of lymphocytes of multiple sclerosis patients grown in the presence of CSF and have demonstrated that there is no specific antigen in CSF to which multiple sclerosis patients' lymphocytes are sensitized. In addition we find that lymphocytes from normal individuals or patients with SSPE do not transform in the presence of measles virus.

Significance to biomedical research and the program of the Institute: Use of frozen-thawed lymphocytes permits us to repeat experiments and to time them and store lymphocytes for future use. Use of monolayers permits more accurate count and allows us to work with lymphocytes without centrifugation or other procedures which disturb and potentially injure

the cell. The proof that there is no specific antigen in normal spinal fluid to which MS patients are sensitized confutes a previous report which added some confusion to the understanding of the pathogenesis of MS.

Proposed course: A survey examination of the transformation reaction in chronic neurological diseases using foreign antigen and host tissue antigens as blastogenic stimuli is continuing.

Honors and Awards: None

Publications: Brody, J.A., Harlem, M.M., Plank, C.R., and White, L.R.: Freezing human peripheral lymphocytes and a technique for culture in monolayers. Science (in press).

Brody, J.A., Harlem, M.M., Kurtzke, J.F., and White, L.R. Unsuccessful attempt to induce transformation by cerebrospinal fluid in cultured lymphocytes from multiple sclerosis patients. New Engl J. Med (in press).

Serial No. NDB (CF) - 66 E 1320
1. Collaborative & Field Research
2. Epidemiology Branch
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1967

Project Title: Stateside Guamanian study

Previous Serial Number: Same

Principal Investigators: Roswell Eldridge, M.D.
Jacob A. Brody, M.D.

Other Investigator: Elizabeth Ryan, R.N.

Cooperating Units: NINDB Research Center, Agana, Guam
School of Public Health, University of California, Berkeley

Man Years

Total:	1/2
Professional:	1/6
Others:	5/12

Project Description:

Objectives: This study was instituted in July 1966 to determine if ALS and PD occur with the same high frequency among Guamanians who have left Guam. Since the bulk of the stateside Guamanians are in California, efforts have been concentrated there.

Methods employed: A household census was completed in the fall of 1967 which included information on neurologic disease. Names of heads of households were obtained from relatives on Guam, the office of the Guamanian representative to Congress, local Guamanians, social organizations, an eight year old NINDB California Guamanian registry and from other Guamanians already living in this country. Household information was obtained by trained Guamanian interviewers living in California and by personnel from the Branch. Follow-up examination of suspect cases of ALS and PD was conducted by specialist physicians.

Major findings: A total of 370 households have been interviewed with demographic and medical information obtained on their 1,853 occupants. Two cases of ALS and two probable cases of PD were found indicating the frequency of these two diseases is similar in this migrant population to that on Guam. Diabetes, gout, renal stone, hypertension and peptic ulcer disease were encountered frequently.

Significance to biomedical research and the program of the Institute: The results suggest that a genetic factor and/or early exposure to an environmental factor is responsible for ALS and PD on Guam. Thus, efforts on Guam should be directed specifically at these two areas.

Proposed course: Evaluation of metabolic and mental disease in this migrant population is being pursued by the School of Public Health, University of California, Berkeley.

Honors and Awards: None

Publications: None

Serial No. NDB (CF) - 66 E 1321
1. Collaborative & Field Research
2. Epidemiology Branch
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Japanese B encephalitis studies on Guam

Previous Serial Number: Same

Principal Investigators: Charles R. Plank, M.D.
Jacob A. Brody, M.D.
C. Joseph Gibbs, Ph.D.
Laboratory of Slow, Latent, and Temperate Viruses

Other Investigators: None

Cooperating Unit: Laboratory of Slow, Latent, and Temperate Viruses, C&FR, NINDB - NDB (CF) - 63 OAD 1140

Man Years:

Total:	3/4
Professional:	1/4
Other:	1/2

Project Description:

Objectives: A Japanese B encephalitis epidemic occurred on Guam in 1947 and 1948. Subsequently there was evidence that the virus completely disappeared from Guam which is almost unprecedented in ARBO virus ecology. Recently a very efficient mosquito vector of JBE the Culex tritaeneorhincus has appeared in large numbers on Guam.

Our studies are divided into three major areas. (1) The long-term neurological and psychological effects of JBE on individuals who suffered from clinical illness and particularly among individuals who suffered from subclinical or inapparent infections. (2) Serological studies of JBE antibodies to determine their persistence and to evaluate the most sensitive methods for detection. (3) To determine if the virus completely disappeared on Guam and, if not, to study the ecology of this agent in an apparently hostile environment.

Methods employed: A large number of sera from humans and animals have been screened against JBE antigen by the hemagglutination inhibition technique. Those positive sera and selected negative ones are also being checked by complement fixation and tissue culture neutralization techniques.

Major findings: Of 492 sera examined, 113 (22.97%) had HI antibody to JBE virus. Of those born before 1950, 106 out of 371 (28.57%) are positive, whereas only 5.79% (7 out of 121) of those born after 1950 have a discernible antibody titer. Complement fixation studies and tissue culture neutralization studies are now underway to determine the specificity or sensitivity of the HI responses.

Significance to biomedical research and the program of the Institute: This project will produce new information on JBE as outlined under "Objectives" by exploiting the unique situation of a single epidemic and subsequent disappearance of JBE on Guam.

Proposed course: It is proposed that when the present laboratory investigations are completed, these specimens be examined with antigens of other viruses of the ARBO B group. Also, when clinical examinations of those people with significant titers are completed, some conclusions can be made about the neurological sequelae of subclinical JBE infections.

Honors and Awards: None

Publications: None

Serial No. NDB (CF) - 66 E 1322
1. Collaborative & Field Research
2. Epidemiology Branch
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Otitis media and hearing loss on Guam

Previous Serial Number: Same

Principal Investigators: Roswell Eldridge, M.D.
Jacob A. Brody, M.D.

Other Investigator: Eldon L. Eagles, M.D.
Assistant Director, NINDB

Cooperating Unit: Office of the Assistant Director, NINDB

Man Years

Total:	2/3
Professional:	1/6
Other:	1/2

Project Description:

Objectives: A three phase study was begun in 1966 to determine the contribution made by otitis media to the high rate of hearing loss on Guam.

Methods employed: 1. 1,541 school children were tested in May 1966 and seven months later those with hearing loss were retested and examined. They were also questioned about ear, nose and throat symptoms and given a physical examination with emphasis on otologic findings.

2. The selective service records of 350 Guamanian men examined in 1966 were reviewed for ear disorders.

3. A one year prospective study beginning in February 1966 on a sample of children born since 1961 was conducted to determine the morbidity from otitis media.

Major findings: 1. Sixteen and eight-tenths percent of those screened had a hearing loss compared to three to five percent of those in U.S. and Canadian studies. More than half of those examined had evidence of otitis media and perforation of the drum was common.

2. More than a third of those examined by selective service on Guam had at least mild hearing loss and one in six of those medically disqualified had severe loss and/or perforation

of the drum, a much higher frequency than in those medically disqualified in the U.S.

3. In contrast to findings in the first two phases, questioning about symptoms of ear infections indicates there is little morbidity related to ear infection in preschool age children.

Significance to biomedical research and the program of the Institute: The unusual pattern of morbidity in this tropical setting suggests that the causative organism and/or the host response may be unique. A major public health compaign would probably be the most effective method to reduce the high rate of otitis media on Guam.

Proposed course: These results have been made known to the Public Health Service of the Government of Guam. This group should best be able to bring this problem to the attention of appropriate medical personnel on the island and to initiate a program of education of parents about the signs of this potentially crippling process. They may also be able to undertake the microbiologic search for the responsible agent.

Honors and Awards: None

Publications: None

Serial No. NDB (CF) - 67 E 1325
1. Collaborative & Field Research
2. Epidemiology Branch
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: One year experience of all births on Guam with special reference to diabetic complications

Previous Serial Number: Same

Principal Investigators: Jacob A. Brody, M.D.
R. Michael Scott, M.D.
Nancy J. Wetmore, R.N.
NINDB Research Center

Other Investigators: Jerome Deutschberger
Office of Biometry
Anne Kantor
Office of Biometry

Cooperating Units: NINDB Research Center, Agana, Guam
Office of Biometry, OD, NINDB

Man Years

Total:	1/4
Professional:	1/12
Other:	1/6

Project Description:

Objectives: The present project was designed to expand the scope of this study by analyzing all births for one year. During the year 1965 there were 2,523 births and we compiled data on date of birth, place of birth, birth weight, birth order, length of gestation, birth defects, age and race of parents, maternal complications such as diabetes, etc.

Methods employed: A study by Yen in 1963-64 revealed an unusually high incidence of abnormal carbohydrate metabolism during pregnancy among the native population of Guam. He also found that obesity and large babies appeared to be a constant finding in mothers with abnormal carbohydrate metabolism and were connected wtih an increased incidence of maternal and perinatal complications.

Major findings: These data are currently being analyzed in order to determine whether the high incidence of diabetes has an appreciable effect on the birth weight.

Significance to biomedical research and the program of the Institute: The data will be of value for public health and anthropological studies.

Proposed course: The data on this project are presently being analyzed.

Honors and Awards: None

Publications: None

Serial No. NDB (CF) - 67 E 1484
1. Collaborative & Field Research
2. Epidemiology Branch
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Acute neurologic disorders coincident with Asian influenza and influenza-like epidemics on Guam

Previous Serial Number: Same

Principal Investigator: Kwang-ming Chen, M.D.

Other Investigators: Jacob A. Brody, M.D.
Samuel Pieper, Jr., M.D.

Cooperating Units: None

Man Years

Total:	1/6
Professional:	1/12
Other:	1/12

Project Description:

Objective: Acute upper respiratory infections occur yearly in the villages on Guam. Some of the illness is caused by influenza. During the 1957 influenza epidemic, Dr. Pieper observed four cases of encephalitis, four cases of aseptic meningitis, and 22 cases of poly or mono-neuritis among 7190 reported flu cases. Observations in subsequent years up to present writing showed there had been definite biannual outbreaks of flu-like epidemic with coincident sporadic reports of acute CNS disorders.

Methods employed: By reviewing medical records available from 1963-1966, seven cases of well-documented acute CNS disorders were collected. The dates of onset were found to be coincident with these biannual outbreaks of "flu-like" epidemic.

Major findings: Fifteen cases of acute CNS disorders and 22 cases of peripheral neuropathies coincident with these epidemics were analyzed in detail in clinical symptoms and laboratory findings. These included eight cases of encephalitis, four cases of aseptic meningitis, three cases of Guillain-Barre syndrome and various peripheral neuropathies. All of these appeared to be associated with influenza infection but none was virologically confirmed.

Significance to biomedical research and the program of the Institute: Further analysis and review led us to the conclusion that without better virologic documentation we had no real contribution.

Proposed course: This project has been discontinued.

Honors and Awards: None

Publications: None

Serial No. NDB (CF) - 67 E 1485
1. Collaborative & Field Research
2. Epidemiology Branch
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Analyses of abnormal urine and blood amino acids metabolism among Guamanians

Previous Serial Number: Same

Principal Investigators: Thomas E. Henson, M.D.
NINDB Research Center
Edward W. Brink, M.D.
NINDB Research Center
Vivian Shih, M.D.
Massachusetts General Hospital

Other Investigators: Jose M. Torres
NINDB Research Center
Manuel T. Cruz
NINDB Research Center

Cooperating Units: NINDB Research Center, Agana, Guam
Amino Acid Laboratory, Massachusetts General Hospital
Boston, Massachusetts

Man Years

Total:	1/6
Professional:	1/12
Other:	1/12

Project Description:

Objectives: Earlier observation indicated that indigenous Guamanians have difficulties in handling protein and carbohydrate. However, the relationship between the observed hyperuricemia and hyperglycemia on Guam and the neurologic manifestations is not clear.

Methods employed: A contract with the Amino Acid Laboratory of the Massachusetts General Hospital for the broad testing for inborn errors of metabolism was securred and blood and urine are being sent to the lab from Guam.

Major findings: None as yet.

Significance to biomedical research and the program of the Institute: This study is contributing to the general knowledge of the Chamorro people of Guam.

Proposed course: This project is continuing.

Honors and Awards: None

Publications: None

Serial No. NDB (CF) - 67 E 1486
1. Collaborative & Field Research
2. Epidemiology Branch
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Dystonia musculorum deformans - a clinical and genetic study

Previous Serial Number: Same

Principal Investigators: Roswell Eldridge, M.D.
Jacob A. Brody, M.D.

Other Investigators: Irving S. Cooper, M.D.
St. Barnabas Hospital
Mennick Goldstein, Ph.D.
New York University
Wolfgang Zeman, M.D.
University of Indiana
Mary Bazelon, M.D.
Childrens Hospital

Cooperating Units: Department of Neurologic Surgery, St. Barnabas Hospital, New York
New York University, New York
Department of Neuropathology, University of Indiana Medical Center, Indianapolis
Childrens Hospital, Washington, D.C.

Man Years

Total:	1
Professional:	2/3
Other:	1/3

Project Description:

Objectives: Dystonia musculorum deformans (DMD) comprises a heterogeous group of conditions characterized by disorder of movement due to either genetic or environmental factors. Earlier studies suggest one form is inherited as an autosomal dominant and that, surprisingly, it is four times more common in those with Jewish ancestry. The present study was undertaken to define further the nosology of these conditions in order to determine the basic defect in each.

Methods employed: Probands with a history of DMD were selected through 14 neurologic and neurosurgical centers and provided the families for study. A detailed family history was obtained stressing geographical origin of ancestral couples and the proband and all available relatives were given

physical examinations. Patients from all areas of the U.S. and treated by various methods were seen to avoid geographic, ethnic, and therapeutic bias.

Major findings: Three-hundred-fifty-three individuals in 73 families have been examined. Ninety-six have dystonia on clinical grounds and an additional 42 who are dead or unavailable are considered affected on the basis of photographs and/or history.

Formal genetic analysis indicates two distinct hereditary patterns: the previously recognized autosomal dominant; and autosomal recessive which has not been recognized heretofore.

An autosomal recessive form of DMD is indicated by at least six observations including the unusual proportion of Jewish families in which DMD occurs in only a single generation and clinical differences between patients in this group and the autosomal dominant group with symptoms in the former tending to appear earlier and to be more severe.

Striking among the clinical aspects of DMD was the high frequency of misdiagnosis of psychiatric illness during the early stages of the disease. At least 21 of the 73 probands had prolonged periods of unrewarding psychotherapy. Notable also was the role of various forms of stress in precipitating or aggravating the symptoms of DMD. Finally, simple intention tremor in ancestors of those with DMD was seen in four Jewish and four non-Jewish families.

The mutation rate for the dominant form is relatively low (approximately one per million gametes). The recessive form of the disease occurs in the Jewish population with a frequency of about one per 40,000 births so that one in 100 in this population is a carrier.

It is imperative that physicians are aware that DMD may exist in at least two different hereditary forms since prognosis and risks to subsequent offspring are different in each.

Significance to biomedical research and the program of the Institute: Elucidation of the fundamental defect in these forms of dystonia will be of practical importance since it should be possible to distinguish between the recessive and dominant forms chemically. The application to genetic counselling of such a test is obvious. As in other inborn errors of metabolism, such a study could provide basic, new information about central nervous system physiology. Parkinson's disease shares certain clinical features with dystonia and is relieved by the same operative procedure so that information gained from the dystonia study may bear on this important problem.

Proposed course: Physiologic and biochemical parameters are being investigated in select families. Preliminary tests on one patient with a varient of DMD suggest a new disorder of intermediary metabolism which is responding to penicillamine therapy.

It is our impression that the IQ is unusually high in patients with the recessive form of DMD. This relationship is being explored in conjunction with the Medical Division of the Board of Education of New York City. If it is true that we are dealing with a gene that affects IQ positively this has dramatic implications and will add further impetus to the search for the chemical expression of the gene.

There are several foci of dystonia in other parts of the world, notably northern Sweden, Israel and southern Italy. Their clinical and genetic study might be equally revealing.

A special report is planned emphasizing the frequent misdiagnosis of early DMD as a psychiatric disorder and the harm this does to patients and their families.

Honors and Awards: None

Publications: None

Serial No. NDB (CF) - 67 E 1487
1. Collaborative & Field Research
2. Epidemiology Branch
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Genetic analysis of family data on Guam ALS cases

Previous Serial Number: Same

Principal Investigators: Roswell Eldridge, M.D.
Kwang-ming Chen, M.D.
NINDB Research Center

Other Investigator: Manuel T. Cruz
NINDB Research Center

Cooperating Unit: NINDB Research Center, Agana, Guam

Man Years

Total:	1/4
Professional:	1/6
Other:	1/12

Project Description:

Objectives: To utilize the accumulation of 20 years of experience for an indepth genetic analysis of pedigree information of Guam ALS.

Methods employed: Pedigrees were developed for the 370 definite cases of Guam ALS by Guamanian practitioners aware of actual biologic parents. Of these 70 were suitable for segregation analysis. Also examination was made of sibs whose parents were both affected by ALS.

Major findings: The initial data indicate that Guam ALS may be inherited as a simple autosomal recessive trait. In 46 families suitable for test of the autosomal recessive hypothesis, 64 cases were observed while 74 cases would be expected from truncate analysis. The 95% confidence limits for such analysis cover the range from 64 cases to 84 cases so the observed number of cases is compatible at this level of significance although barely so.

Two of 13 over 35 years of age whose parents both had ALS were found to have signs compatible with early ALS. If ALS is recessive all such offspring should eventually be affected.

In testing for the autosomal dominant hypothesis in the 16 families suitable for this analysis, nine cases were observed, 27 would be expected and 19 to 35 cases would be the range at a 95% limit

confidence. Therefore, autosomal dominant inheritance is possible only if one postulates the gene is not penetrant (i.e., there is no expressing of the disease) in 50% to 70% of those carrying it.

Troublesome to any simple mode of inheritance postulated is the 2:1 male to female ratio of ALS patients A finding which may answer this discrepancy and possibly shed light on the basic process of the disease is that in these siblings there is an excess of female deaths under one year of age.

Significance to biomedical research and the program of the Institute: Obviously establishing a genetic basis for Guam ALS would have far-reaching consequences. The elusive question of the cause of Guam ALS would be answered. A new genetic disease would be added to the expanding catalogue of inherited neurologic diseases. Efforts of the Branch on Guam could be concentrated on other problems such as the PD question and its relation to the pattern of metabolic disease on the isalnd. A search could be made for other isolated populations where the gene might also be frequent.

Proposed course : Complete information is being obtained on pedigrees of other Guam ALS cases so as to increase the sample studied. Detailed study of offspring now at risk of specific mating types is underway.

Since a number of Filipinos of Guam have ALS and in the past the Filipinos were a major source of repopulation of the isalnd, a search for an ALS focus on Luzon will be made.

A similar genetic analysis of PD will be undertaken.

Honors and Awards: None

Publications: None

Serial No. NDB (CF) - 67 E 1488
1. Collaborative & Field Research
2. Epidemiology Branch
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Serological studies of common viruses and genotyping in cases of multiple sclerosis (MS) and controls

Previous Serial Number: Same

Principal Investigators: Thomas E. Henson, M.D.
Jacob A. Brody, M.D.
John L. Sever, M.D.
Perinatal Research Branch, NINDB

Other Investigators: Mark Dyken, M.D.
Neurology Department, Indiana University Medical Center
A. Donald Merritt, M.D.
Department of Medical Genetics, Indiana University Medical Center
Jerome Deutchberger
Office of Biometry, NINDB
Anne Kantor
Office of Biometry, NINDB

Cooperating Units: Section of Infectious Diseases, PRB, NINDB
Neurology Department, Indiana University Medical Center, Indianapolis
Department of Medical Genetics, Indiana University Medical Center, Indianapolis
Office of Biometry, OD, NINDB

Man Years

Total:	2-1/6
Professional:	1-1/6
Other:	1

Project Description

Objectives: To test the hypothesis that MS may be causes by an unusual response to a common virus infection. To search for possible distortions of segregation and association between MS and one or more genetic markers.

Methods employed: MS patients known to the Neurology Department, IUMC and to the Indiana Chapter of the National Multiple Sclerosis Society were

contacted and asked to participate. In addition for each case several controls with similar backgrounds and infectious disease experience were selected. Suitable controls are: sibling near the age of the patient, a classmate friend of the patient who grew up in the same community, and the patient's spouse. All patients used in the study were personally examined by one of the two clinical neurologists participating in the study to verify the diagnosis. Patients and controls answered standard questions regarding infectious disease, environment, course of illness and family history and blood specimens were taken.

Serological analysis is being conducted in the Section of Infectious Diseases, PRB, NINDB using a battery of common virus antigens by hemagglutination and complement fixation methods. Differences between the patient and his controls and similarities among the patients will be sought.

Genotyping is being done by the Department of Medical Genetics, IUMC for approximately 20 polymorphic systems including blood groups, erythrocytic enzyme and serum protein evaluations.

A portion of the frozen serum is being banked to test promising hypotheses in the future.

Major findings: Data are being analyzed.

Significance to biomedical research and the program of the Institute: The serological studies whether results are positive or negative will give valuable information regarding the role of viruses in the etiology of MS. Adequate genotyping of MS patients and their families has not been reported. The proclivity to develop MS may be associated with a testable genetic marker.

Proposed course: The project will be terminated upon completion of analyses.

Honors and Awards: None

Publications: None

Serial No. NDB (CF) - 67 E 1489
1. Collaborative & Field Research
2. Epidemiology Branch
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Neuropathological studies in veterans dying of ALS who served on Guam

Previous Serial Number: Same

Principal Investigators: Thomas E. Henson, M.D.
Jacob A. Brody, M.D.
R. Michael Scott, M.D.

Other Investigators: Kenneth Earle, M.D.
Armed Forces Institute of Pathology
Asao Hirano, M.D.
Montefiore Hospital
Joseph Seggora, M.D.
Veterans Administration Hospital
F. A. Quadfasel, M.D.
Veterans Administration Central Office

Cooperating Units: Neuropathology Branch, Armed Forces Institute of Pathology, Washington, D.C.
Department of Neuropathology, Montefiore Hospital New York
Veterans Administration Hospital, Boston
Neurology Section, Veterans Administration Central Office, Washington, D.C.

Man Years

Total:	1/3
Professional:	1/3
Other:	0

Project Description:

Objectives: To determine if ALS in veterans who served on Guam is an acquired disease.

Methods employed: Dr. Hirano has reported characteristic neurofibrillary changes in Guamanian ALS patients, but these changes are not seen in classical stateside ALS. Since a large number of U.S. servicemen were stationed on Guam during World War II, it is possible to examine the CNS of U.S. veterans who died of ALS who spent considerable time on Guam. The question to be answered is whether these men show the characteristic Guam-type neuropathological

changes or the classical stateside ALS changes. A search for suitable material from the AFIP files and veterans hospital files is being conducted. When approximately five brains from veterans dying of ALS serving on Guam and five brains from control cases dying of ALS who were not on Guam are found, the three collaborating neuropathologists will review the material independently.

Major findings: Suitable neuropathologic material is still being collected. We have acquired two brains from veterans dying of ALS with known service on Guam; however, the Veterans Administration hospital sources have now been exhausted. We have subsequently contacted 13 major neuropathology institutes in the country requesting similar autopsy material and have received names of 40 additional ALS cases. These names are currently being processed by the V.A. to determine if these patients had spent any time on Guam. From the V.A. material, there are a large number of control cases available.

Significance to biomedical research and the program of the Institute: If Guamanian type pathological changes are found in veterans who served there, it would indicate that perhaps they acquired ALS from their Guam exposure.

Proposed course: When three additional specimens are collected, the study will be rapidly completed.

Honors and Awards: None

Publications: None

Serial No. NDB (CF) - 67 E 1490
1. Collaborative & Field Research
2. Epidemiology Branch
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Flourescent microscopy using fixed, imbedded CNS tissue

Previous Serial Number: Same

Principal Investigators: Charles R. Plank, M.D.
Paul Albrecht, M.D.
Special Chronic Disease Studies

Other Investigator: None

Cooperating Unit: Special Chronic Disease Studies, C&FR, NINDB

Man Years

Total:	1/3
Professional:	1/4
Other:	1/12

Project Description:

Objectives: The objective in this project was to determine if Carnoy-fixed paraffin-imbedded tissues are satisfactory for immunoflourescent microscopy. If so, this would have offered advantages in storage, convenience, and in safety when working with virulent and/or unknown agents.

Methods employed: CNS tissue infected wtih ARBO A, ARBO B, certain Coxsackie strains, Herpes simplex, lymphocytic choriomeningitis, rabies, and mumps viruses were fixed with Carnoy's solution and imbedded in paraffin. Duplicate specimens were frozen and stored at -70°C. Examples of each specimen were sectioned in an appropriate manner, stained and then compared for quality, quantity, and specificity by immunoflourescent techniques. (This technique has been previously described by Dr. Albrecht using certain ARBO B viruses.)

Major findings: This technique was not adequate for work with these agents.

Significance to biomedical research and the program of the Institute: If the technique of using fixed, imbedded tissues had been found satisfactory, it would have offered a great number of advantages of convenience and safety in collecting, storage, and handling infected and noninfected specimens intended for flourescent microscopic examination.

Proposed course: This study has been terminated.

Honors and Awards: None

Publications: None

Serial No. NDB (CF) - 67 E 1494
1. Collaborative & Field Research
2. Epidemiology Branch
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Influence of diurnal variation on tonometric surveys

Previous Serial Number: Same

Principal Investigator: Richard E. Goldberg, M.D.

Other Investigators: J. Theodore Schwartz, M.D.
Allen R. Lewis, M.S.
Biometrics Branch, C&FR, NINDB

Cooperating Unit: Biometrics Branch, C&FR, NINDB

Man Years:

Total:	1/6
Professional:	1/12
Other:	1/12

Project Description:

Objectives: To study the population trend of average intraocular pressure at different hours of the day.

In normal eyes and in eyes with glaucoma, the level of intraocular pressure does not remain constant throughout the day. Several different patterns of diurnal variations have been described. If total populations show a significant overall variation in diurnal patterns such variation could influence the outcome of tonometric surveys designed to collect comparable epidemiologic data as well as the outcome of surveys undertaken to identify glaucoma suspects.

Methods employed: In this project the measurements of intraocular pressure on 2,620 eyes as obtained in three community surveys (Nesquehoning, Penn., Colorado River Reservation, Arizona, and Salt River Reservation, Arizona) were analyzed to determine the possible existence of a significant population trend in diurnal variation. For each community, intraocular pressure measurements obtained by three different examination techniques are being analyzed separately.

Major findings: Analysis shows lowered pressure for those measurements taken later in the day. This trend has been consistent for each of the communities and was found to be statistically significant. This tendency

is consistent with clinical knowledge of diurnal variation although the present data do not permit descrimination between an age effect and diurnal variation as an explanation of the findings.

Significance to biomedical research and the program of the Institute: The findings of the study suggest that the time of measurement can influence comparability of tonometry data collected for epidemiologic investigation.

Proposed course: This project will continue.

Honors and Awards: None

Publications: None

Serial No. NDB (CF) - 67 E 1495
1. Collaborative & Field Research
2. Epidemiology Branch
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Remote neurological effects of lung cancer

Previous Serial Number: None

Principal Investigator: Elliot C. Wilner, M.D.

Other Investigator: None

Cooperating Unit: Veterans Administration

Man Years

Total:	1/2
Professional:	1/2
Other:	0

Project Description:

Objectives: To determine if lung cancer produces distinct syndromes of involvement of the nervous system, and if so, to determine the role and relationship between the histologic type of cancer and the various neurological syndromes.

Methods employed: The study group consisted of 106 patients from V.A. hospitals who had had the diagnosis of lung cancer made by biopsy (or by sputum cytology if biopsy confirmation was to be had later). These subjects were seen either as inpatients or as outpatients followed in clinics. The control groups consisted of 44 inpatients at the Washington, D.C. V.A. Hospital who were hospitalized for various subacute or chronic pulmonary diseases and considered not to have carcinoma. The study and control groups were roughly matched for age, duration of illness, consumption of alcohol and tobacco.

All subjects in the study and control groups were interviewed and examined neurologically. The interview served to document information about duration of illness, type of therapy, social habits, and previous illnesses, and to elicit symptoms of current neurological disease. The examination was designed to uncover signs of any of the syndromes previously ascribed to remote malignancies.

Blood specimens were obtained from six patients and may be obtained from more patients later for lymphocyte transformation studies and to be used for innoculation into laboratory animals.

Major findings: No statistically significant differences in the rate or type of unexplained neurological signs were found between cancer patients and controls; the rate among the controls was much higher than that reported in previous series. Among the cancer patients we did not find the frequency of unexplained neurological signs to be independent of duration of cancer symptoms or treatment, as has been stated, but in fact with successful treatment and increased survival time the frequency declined. Finally, we did not find in this small series that oat cell carcinoma was associated with a high frequency of the myasthenic syndrome or severe peripheral neuropathy. The impression gained was that the majority of the remote neuropathies represent a nonspecific injury to the neuromuscular apparatus as a result of nutritional, endocrinological, immunological, or metabolic disturbances, and they occur in many chronic diseases including carcinoma of the lung.

Significance to biomedical research and the program of the Institute: See above.

Proposed course: This project has been completed.

Honors and Awards: None

Publications: Wilner, E.C. and Brody, J.A.: An evaluation of the remote effects of cancer on the nervous system. Neurology (in press).

Serial No. NDB (CF) - 67 E 1496
1. Collaborative & Field Research
2. Epidemiology Branch
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Sequelae of measles

Previous Serial Number: Same

Principal Investigator: Elliot C. Wilner, M.D.

Other Investigator: Joyce M. Cannon, R.N.

Cooperating Units: Fort Belvoir, Virginia
Office of Biometry, OD, NINDB

Man Years

Total:	2/3
Professional:	1/3
Other:	1/3

Project Description:

Objectives: To test the hypothesis that a subclinical encephalopathy occurs with measles infection and may cause neurological sequelae, particularly in those cases in which infection occurred under the age of two years.

Methods employed: A current list of all students in the 4th, 5th, 6th, and 7th grades at the Fort Belvoir, Virginia military base was compiled, and a questionnaire was sent to the parents of each which requested information regarding their child's history of infectious diseases, including rubeola, rubella, varicella, roseola, mumps, and scarlet fever. They were asked to give details for each disease as to age at infection, visit to a physician, hospitalization, and complications. Approximately 1,000 questionnaires were distributed and the response was nearly 90%.

This inquiry yielded 77 cases in which the child was said to have had measles at 24 months or less, including 14 at 12 months or less. These 77 were matched by an equal number of control cases who had measles some time after age 2. The number of children actually examined was 12 who had measles at 12 months or less, 40 who had measles at 24 months or less, and, as controls, 80 who had measles some time after age 24 months. Neurological examinations on all the subjects and controls were conducted "blind," using a modified form of the Perinatal Research Branch seven-year pediatric-neurologic protocol. Information regarding height, weight, visual acuity, and audiometric testing was obtained from school health records. Information regarding IQ tests, grade placement tests, and classroom

deportment was obtained from school records.

An attempt was made to validate the data obtained from the questionnaires by reviewing medical files at the Base Hsopital. This proved to be unfeasible since many children's records had not been forwarded and of the ones available the majority contained no record of a visit to a physician for the diseases under study.

Major findings : Of the total of 132 children examined, there were 41 who were found to have one or more "soft" neurologic signs. These cases were distributed in nearly equal proportions among the study groups and the controls, so that subclinical encephalitis from measles was not demonstrated by a postulated higher frequency of sequelae among those who were infected at a very young age. One positive finding of the study was that the occurrence of "soft" signs does correlate with lower scores on IQ tests and classroom deportment. The 41 children with "soft" signs had a mean total IQ of 106.2, compared to the 91 children without any neurologic signs who had a mean IQ of 112.1. Another positive finding was that mixed laterality, or incomplete cerebral dominance, is significantly more frequent among children who have "soft" signs than among those who do not, occurring in 49% of cases compared to 20%.

Significance to biomedical research and the program of the Institute: See above.

Proposed course: This project has been completed and a manuscript is being prepared.

Honors and Awards: None

Publications: None

Serial No. NDB (CF) - 67 E 1497
1. Collaborative & Field Research
2. Epidemiology Branch
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Guillain-Barre (GB) - Bell's palsy (BP) study

Previous Serial Number: Same

Principal Investigator: Elliot C. Wilner, M.D.

Other Investigator: None

Cooperating Unit: None

Man Years

Total:	1/24
Professional:	1/24
Other:	0

Project Description:

This project was abandoned.

Honors and Awards: None

Publications: None

Serial No. NDB (CF) - 68 E 1593
1. Collaborative & Field Research
2. Epidemiology Branch
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: The prognosis of general paresis after penicillin treatment

Previous Serial No.: None

Principal Investigator: Elliot C. Wilner, M.D.

Other Investigator: Jacob A. Brody, M.D.

Cooperating Unit: St. Elizabeth's Hospital, Washington, D.C.

Man Years:

Total:	1/2
Professional:	1/3
Other:	1/6

Project Description:

Objectives: To determine if there is a difference in the prognosis of general paresis after treatment with penicillin compared with other forms of treatment.

Methods employed: 100 patients at St. Elizabeth's Hospital diagnosed as having general paresis, and who satisfied our criteria of having been treated for the disease at least 10 years previously, comprised our study population. Patients were divided into three groups according to whether they were treated with penicillin alone, penicillin and malaria, or malaria or other unspecified treatment. Charts of the patients were then reviewed for evidence of neurological signs which developed only subsequent to treatment and which had no clear or likely cause other than progression of neurosyphilis. No attempt was made to evaluate any mental or neurological signs which were present before therapy. In each case, the type and amount of treatment for general paresis, as well as the results of serological and spinal fluid examinations were recorded.

Major findings: Gross evidence of progression of neurosyphilis appeared in 31 patients, whose average age was 53.1 years and average interval after treatment was 12.1 years. Among the various treatment groups the "malaria or other" patients had the lowest frequency of progression, 17% which probably implies that time had selected them as the most stable cases from among a much larger number of patients. Evidence of progression appeared in 39% of all those who received penicillin. There was not a tendency

toward a lower frequency of progression among patients receiving higher doses of penicillin. Progression usually occurred without reactive changes in the spinal fluid, and conversely, reactive changes in the spinal fluid did not always presage clinical progression.

Significance to biomedical research and the program of the Institute: The conclusion reached was that many of the neurologic complications occurring late in the course of treated general paresis probably reflect irreversible changes sustained before treatment, and it is unlikely that penicillin or any other treatment can completely prevent progression of the disease.

Proposed course: This project has been completed.

Honors and Awards: None

Publications: Wilner, E. and Brody, J.A.: The prognosis of general paresis after penicillin treatment. JAMA (in press).

Serial No. NDB (CF) - 68 E 1594
1. Collaborative & Field Research
2. Epidemiology Branch
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: The frequency of extrapyramidal and lower motor neuron disease in demented patients

Previous Serial No.: None

Principal Investigator: Elliot C. Wilner, M.D.

Other Investigators: Richard Goldberg, M.D.
Jacob A. Brody, M.D.

Cooperating Unit: St. Elizabeth's Hospital, Washington, D.C.

Man Years:

Total:	1/2
Professional:	1/2
Other:	0

Project Description:

Objectives: To explore the incidence and type of extrapyramidal and lower motor neuron involvement in patients with nonspecific dementing illness, and to determine if there are syndromes which resemble the parkinsonism-dementia disease of Guam.

Methods employed: 206 patients were studied who satisfied the criteria for selection of having acquired dementia of unproven etiology (including cases diagnosed as cerebral arteriosclerosis, senile dementia, Alzheiner's disease, etc.), with no known cause of extrapyramidal or lower motor neuron disease, and at least 35 years of age. These patients were examined neurologically for the presence of uppper motor neuron, lower motor neuron, extrapyramidal and cerebellar signs. Their hospital records were examined for data on age, race, diagnosis, length of hospitalization, and phenothiazine administration. Patients with the most impressive extrapyramidal disease were to be followed to time of death, when post-mortem examination would be sought.

Major findings: Extrapyramidal signs were frequently encountered, including in various combinations, 19 cases of resting tremor, 6 cases of chorea or athetosis, 18 cases of cogwheel rigidity, and 16 cases of plastic rigidity. Bradykinesia was difficult to assess in many patients who were quite lethargic, and in many other patients voluntary movements seemed to suffer from apraxia. Masking of facial expression was also difficult to

assess because of the apathetic condition of many patients. Gait marked by loss of associated movement was seen in 25 patients. In all, there were 28 patients (14%) whose combination of extrapyramidal signs was felt to denote parkinsonism, and only 12 of them were being treated currently with any phenothiazine drug.

An additional finding was that 65 patients (31%) had either complete loss or marked impairment of supraversion (upward conjugate gaze). This finding was then investigated further in schizophrenic patients as well as in chronic brain disease patients, and also in normal controls.

Significance to biomedical research and the program of the Institute:

Proposed course: The data from this investigation is in the process of further analysis. One hypothesis to be explored is that certain signs commonly attributed to basal ganglia disease may in demented patients actually be mimicked by signs of the cerebral cortical disease. Another hypothesis to be explored is that impairment of vertical conjugate gaze represents a frequent sign of cerebral cortical disease.

Honors and Awards: None

Publications: None

Serial No. NDB (CF) - 68 E 1595
1. Collaborative & Field Research
2. Epidemiology Branch
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: An evaluation of the effect of successful thalamic surgery on the progress of unilateral Parkinson's Disease

Previous Serial No.: None

Principal Investigators: R. Michael Scott, M.D.
Jacob A. Brody, M.D.
Joyce M. Cannon, R.N.

Other Investigators: Irving S. Cooper, M.D.
St. Barnabas Hospital
Mary Bazelon, M.D.
Children's Hospital
Robert S. Schwab, M.D.
Massachusetts General Hospital
David Poskanzer, M.D.
Massachusetts General Hospital

Cooperating Units: Department of Neurosurgery, St. Barnabas Hospital
Bronx, New York
Department of Neurology, Massachusetts General Hospital, Boston
Children's Hospital, Washington, D.C.

Man Years:

Total:	1
Professional:	11/12
Other:	1/12

Project Description:

Objectives: To evaluate Dr. Cooper's hypothesis that in patients with unilateral Parkinson's Disease, thalamic surgery which succeeds in permanently abolishing the tremor and rigidity on the involved side will either stop or markedly delay the appearance of the symptoms on the other side of the body; and to determine the natural history of unilateral Parkinson's Disease.

Methods employed: The charts of 1,700 consecutive thalamic surgical cases from January 1963 through September 1964 at St. Barnabas Hospital were reviewed to select 100 patients who came to surgery with symptoms of tremor and rigidity confined to one side of the body. Each of these patients is being contacted and given an interview and examination to

determine the subsequent course of the disease. Two control groups are being obtained. The first of these consists of 30 patients who presented to Dr. Cooper with unilateral signs, who were accepted for surgery, but for various resons were not operated upon. The second control group will consist of patients seen by Dr. Schwab in Boston and subsequently treated medically; they will be matched with the operated population for age, sex, and duration of symptoms.

Major findings: Thirty patients have been seen thus far, including nine control patients. It is too early to draw conclusions, but there appears to be a form of Parkinson's Disease that remains unilateral, with or without successful surgical intervention. Several patients have been seen in whom tremor and rigidity were completely abolished by surgery but whose symptoms nevertheless spread to the opposite side several years after survery.

Significance to biomedical research and the program of the Institute: Showing that the disease process can be altered by successful surgery would strongly indicate that surgery should be performed as early as possible in the course of Parkinson's Disease. This study will also contribute to knowledge of the natural hisotry of unilateral Parkinson's Disease.

Proposed course: We will continue to examine the operated patients and the first control group; with selection and examination of the second matched control group, the study will be completed in the fall of 1968.

Honors and Awards: None

Publications: None

Serial No. NDB (CF) - 68 E 1596
1. Collaborative & Field Research
2. Epidemiology Branch
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Toxoplasma antibody in astrocytoma patients

Previous Serial No.: None

Principal Investigators: R. Michael Scott, M.D.
Jacob A. Brody, M.D.

Other Investigators: None

Cooperating Units: The Departments of Neurosurgery at
Temple Unilversity, Philadelphia
University of Pennsylvania, Philadelphia
The Johns Hopkins University, Baltimore
National Naval Medical Center, Bethesda
Georgetown University, Washington, D.C.
Montefiore Medical Center, New York

Man Years:

Total:	1/2
Professional:	1/2
Other:	0

Project Description:

Objectives: To determine (1) whether astrocytoma patients have significant serum toxoplasma antibody; (2) whether the antibody is related to the histologic grade of the tumor.

Methods employed: Schuman et al., (Amer J. Pub Health 57:848-856, 1967) noted the association of CNS astrocytomas and toxoplasma antibody; however, their cases were not broken down into grades. This paper was of particular interest to us in that gliomas have been experimentally produced in chickens by innoculations of toxoplasma (Erichsen, S. and Harboe, A.: Acta Path. et Microbiol. Scandinav. 33:381-386, 1953). Therefore, we are obtaining serum specimens from patients with astrocytomas of all grades, postulating that the lower grade, cystic astrocytomas may have resulted from toxoplasma infection.

Major findings: 35 specimens have been collected to date. Analysis of the serums for toxoplasma antibody will be performed when 100 specimens have been obtained.

Significance to biomedical research and the program of the Institute: If significant toxoplasma antibody is found in the sera of astrocytoma patients, the association merits additional laboratory investigations. It is possible that a depressed immune response in these patients resulted in the toxoplasma infection, which would indicate the need for additional serological testing in patients with the other types of neoplasia. Should antibody be associated with the benign low grade astrocytomas, an etiological role for the toxoplasma organism could be postulated.

Proposed course: We are continuing to collect patient sera from the Cooperating Units named above. In addition, we are discussing with the Brain Tumor Chemotherapy Branch of the NCI in Baltimore the possibility of obtaining serial toxoplasma antibody from patients undergoing therapy in order to determine if their patient's altered immune responses result in a higher incidence of toxoplasma infection.

Honors and Awards: None

Publications: None

Serial No. NDB (CF) - 68 E 1597
1. Collaborative & Field Research
2. Epidemiology Branch
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Hyperreflexia and spastic paralysis among New Caledonian lepers

Previous Serial No.: None

Principal Investigators: Jacob A. Brody, M.D.
Yoshiro Yase, M.D.
Wakayama Medical College
Gerard Chemier, M.D.
Institut-Pasteur
Yves Philippe, M.D.
Hopital Gaston Bourret

Other Investigators: None

Cooperating Units: Division of Neurological Diseases, Wakayama Medical College, Wakayama, Japan
l'Institut-Pasteur, Noumea, New Caledonia
Service de Neuro-Psychiatrie, l'Hoptial Gaston Bourret, Noumea, New Caledonia

Man Years:

Total:	1/4
Professional:	1/4
Other:	0

Project Description:

Objectives: To determine if a syndrome of spastic paraplegia exists among New Caledonian lepers. To determine if the disease is confined to Melanesians, to lepers and if it resembles other neurologic syndromes which we are following in the Pacific area.

Methods employed: A field trip was made to New Caledonia where European and native lepers and control individuals with tuberculosis were studied by history and physical examination.

Major findings: The syndrome of spastic paraplegia and hyperreflexia does occur apparently exclusively among New Caledonian lepers both of European and native origins.

Significance to biomedical research and the program of the Institute: Leprosy is known to cause peripheral neuropathy and has never been associated with syndromes involving hyperreflexia and aspatic paraglegia. This documentation of the occurrence of this syndrome is therefore of great interest since it implies that this clinical entity is superimposed upon the basic neuropathology of leprosy. Whether it is a form of drug reaction or a toxic or dietary imbalance is not clear.

Proposed course: We do not contemplate any immediate follow-up of this study.

Honors and Awards: None

Publications: Brody, J.A., Yase, Y., Chemier, G., and Philippe, Y.: Hyperreflexia and spastic paralysis among New Caledonian lepers. Amer. J. Trop. Med. Hygiene (in press).

Serial No. NDB (CF) - E 68 1598
1. Collaborative & Field Research
2. Epidemiology Branch
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Epilepsy on Guam

Previous Serial No.: None

Principal Investigators: Thomas E. Henson, M.D.
NINDB Research Center
Edward W. Brink, M.D.
NINDB Research Center

Other Investigators: Jacob A. Brody, M.D.
Manuel Cruz
NINDB Research Center
Jose Torres
NINDB Research Center
Francisco Leon Guerrero
NINDB Research Center

Cooperating Unit: NINDB Research Center, Agana, Guam

Man Years:

Total:	1/2
Professional:	1/4
Other:	1/4

Project Description:

Objectives: To determine the incidence and prevalence of epilepsy on Guam. To investigate methods for field studies of epilepsy. To determine if previous reports of unusually high incidence of convulsive disorders on Guam are accurate.

Methods employed: We are testing four basic approaches: (1) we are following-up a 1962 survey of convulsive disorders in Umatac and Merizo to determine the outcome of those children known to have had febrile convulsions 6 to 8 years ago; (2) to determine the true incidence and prevalence in a sample population we are doing a house by house survey in the villages of Talofofo, Merizo, and Yona; (3) as referral neurologists on Guam we are updating all previous referrals of convulsive disorders to us and establishing a registry. To add to this registry we are contacting all medical and paramedical personnel on Guam to discover new cases. This registry will be permanent and permit us to conduct studies in the Guam population; (4) to further elaborate on methods for acquiring information we are following-up all births on Guam in 1958 and 1963 throughout the entire island to determine the rates of convulsive disorders in these preselected populations.

Major findings: None as yet.

Significance to biomedical research and the program of the Institute: Further studies of epilepsy in a well defined and accessible population will add to the understanding of this disease and contribute new information concerning epilepsy in a tropical environment. It will also yield important information on different survey techniques and their relative accuracy.

Proposed course: The data will be analyzed as soon as it is available and more detailed studies of epilepsy will develop from our basic information.

Honors and Awards: None

Publications: None

Serial No. NDB (CF) - 68 E 1599
1. Collaborative & Field Research
2. Epidemiology Branch
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Relation of environmental and social factors to vascular disease mortality in Washington County, Maryland

Previous Serial No.: None

Principal Investigator: Robert E. Markush, M.D., M.P.H.

Other Investigator: George Comstock, M.D.
Johns Hopkins

Cooperating Unit: Johns Hopkins School of Hygiene and Public Health
Training Center for Public Health Research,
Hagerstown, Maryland

Man Years

Total:	1/6
Professional:	1/12
Other:	1/12

Project Description:

Objectives: The objective of this study is to determine the relationship between selected environmental and social factors in the subsequent occurrence of death from strokes and other major vascular diseases.

Methods employed: The study consists of relating data collected by the Johns Hopkins School of Hygiene and Public Health Training Center for Public Health Research in a 1963 census of Washington County to data on death certificates in the three following years. The census data are available on data processing cards. The study, therefore, consists of transferring the mortality data to electronic tape, editing the tapes, designing tables, and analyzing the results.

Major findings: None

Significance to biomedical research and the program of the Institute: Relating the occurrence of strokes to such factors as marital status, education, cigarette smoking, and other environmental factors may provide suggestions to etiology. Comparison of factors associated with strokes and factors associated with other major vascular diseases such as

myocardial infarction may throw additional light on the etiology and prevention of strokes.

Proposed course: By the end of April 1968, preliminary runs should be available which will indicate the frequencies of the variables of interest both in the census data and in the mortality data. It is anticipated that a final report should be available by the end of 1968.

Honors and Awards: None

Publications: None

Serial No. NDB (CF) - 68 E 1600
1. Collaborative & Field Research
2. Epidemiology Branch
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Development of techniques for epidemiologic study of convulsive disorders

Previous Serial No.: None

Principal Investigator: Robert E. Markush, M.D., M.P.H.

Other Investigators: J. Kiffin Penry, M.D.
Section of the Epilepsies, C&FR, NINDB
R. Michael Scott, M.D.
Jacob A. Brody, M.D.

Cooperating Units: Section on the Epilepsies, C&FR, NINDB
Department of Preventive Medicine, College of Medicine, Howard University, Washington, D.C.
Children's Hospital, Washington, D.C.

Man Years

Total:	5/12
Professional:	1/4
Other:	1/6

Project Description:

Objectives: The object of this study is to develop techniques for the epidemiologic study of convulsive disorders in different populations.

Methods employed: The assumption is made that the tendency toward convulsive disorders is a continuum in the general population. A questionnaire was developed to elicit a history of those symptoms clinically suspected of being common among those with convulsive disorders. The questionnaire was tested on two populations: a population of approximately 100 known epileptics from Children's Hospital and a second population of approximately 100 children born in 1962 at Freedmen's Hospital, Washington, D.C. The questionnaires were mailed by Howard University, College of Medicine, to the parents of all those children.

Major findings: The questionnaire succeeded in every case of known convulsive disorder in making the diagnosis properly. Of the 22 respondents from the Freedmen's Hospital population, 13 had one or more positive answers to the symptom questions. These are currently being examined to determine the significance to the positive responses.

Significance to biomedical research and the program of the Institute: Epidemiologic studies of epilepsy to date have been able to utilize only diagnoses made by practicing physicians in a given community. For this reason, they have been completely dependent upon the quality of medical diagnosis in the given community. This dependence has limited the opportinity to make comparisons of epilepsy prevalence in different populations. If it is possible to develop a technique for measuring comparably the prevalence of symptoms related to convulsions, it should be possible to do epidemiologic comparisons in a variety of populations. Such epidemiologic studies would then be able to indicate factors related to the occurrence of convulsive disorders and possibly suggest methods for their prevention.

Proposed course: Neurological examinations will be conducted on the 13 positive cases from the Freedmen's Hospital normal population. Once these are completed, the data collection phases of the study will be over. A report indicating both the utility of the questions included in this study as well as the factors affecting response rates to the questionnaire will be written. The report should be completed by the end of June 1968.

Honors and Awards: None

Publications: None

Serial No. NDB (CF) - 68 E 1601
1. Collaborative & Field Research
2. Epidemiology Branch
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: The epidemiology of convulsive disorders in Washington County, Maryland

Previous Serial No.: None

Principal Investigator: Robert E. Markush, M.D., M.P.H.

Other Investigator: J. Kiffin Penry, M.D.
Section on the Epilepsies, C&FR, NINDB

Cooperating Units: Johns Hopkins School of Hygiene and Public Health
Training Center for Public Health Research,
Hagerstown, Maryland
Washington County Health Department, Hagerstown
Section on the Epilepsies, C&FR, NINDB

Man Years:

Total:	1/4
Professional:	1/6
Other:	1/12

Project Description:

Objectives: The objectives of this study are to determine the relationships between selected environmental and social factors and the prevalence of convulsive disorders in Washington County; to demonstrate the feasibility and significance of new epidemiologic techniques for the investigation of convulsive disorders; and to determine the degree to which convulsive disorders are undiagnosed in a community.

Methods employed: Records of all cases of convulsive disorders in the County Clinic at Hagerstown will be abstracted. In addition, all practicing physicians in Washington County will be asked to give the name, address, and other identifying data on their patients who have convulsive disorders. These cases will represent the known patients with convulsive disorders in the community. Cases of all ages will be included in this survey. In a second survey, a screening questionnaire will be mailed to the parents of all children in the 3rd grade of school. For nonrespondents to the questionnaire, telephone interviewing and home visits will be made. It is anticipated that approximately 2,000 children will be surveyed. Using the questionnaire, 100 children with the greatest number of positive responses, 100 children who are completely negative, and 100 children from the intermediate group will be selected for

follow-up physicial examinations which will include a detailed neurological examination and electro-encephalogram.

Major findings: None

Significance to biomedical research and the program of the Institute: Demonstration of a feasible method to study the epidemiology of convulsive disorders in populations which may vary in their medical coverage will permit the investigation of epilepsy in many different communities and make it more likely that significant etiologic factors may be discovered. The study also should produce some substantive information on factors associated with the development of convulsive disorders, and should provide a very rough estimate of the degree to which convulsive disorders may be unrecognized in a community.

Proposed course: This study cannot begin until cleared by the Bureau of the Budget, and until contracts are developed. It is estimated that the study may begin in September, 1968. Physical examinations of the 300 children should be completed by the following summer.

Honors and Awards: None

Publications: None

Serial No. NDB (CF) - 68 E 1602
1. Collaborative & Field Research
2. Epidemiology Branch
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Comparative epidemiology of major vascular diseases

Previous Serial Number: None

Principal Investigator: Robert E. Markush, M.D., M.P.H.

Other Investigators: None

Cooperating Unit: None

Man Years

Total:	1/3
Professional:	1/4
Other:	1/12

Project Description:

Objectives: The objective of this study is to determine the association of strokes with a number of demographic factors, utilizing data that have been collected by others, but not analyzed. A secondary objective is to indicate the kinds of epidemiologic data that are presently in greatest need.

Methods employed: Data have been collected from published and unpublished sources and are being analyzed using recently developed epidemiologic techniques which related prevalence of conditions in the living population to prevalence in decedents.

Major fidnings: The first subject analyzed in this study is the effect of sex on the prevalence of the major vascular diseases. Sex has been chosen as the first variable because of the striking difference in male/female ratios between coronary artery disease and strokes. Preliminary findings suggest that hemorrhagic strokes closely resemble hypertensive disease in their epidemiologic patterns and that thrombotic strokes closely resemble coronary disease.

Significance to biomedical research and the program of the Institute: Clarification of the relationship of strokes to other major vascular diseases should give us a better understanding of the causation of strokes. If it can be shown, for example, that thrombotic stroke deaths have similar associations as coronary disease deaths, then programs directed at preventing coronary disease may have similar effects upon thrombotic strokes. Similarly, programs

to control hypertension may be able to reduce considerably hemorrhagic stroke mortality.

Proposed course: A paper on the relationship between sex and vascular diseases should be completed by June. Additional papers on ethnic and geographic distribution of stroke and vascular disease mortality will follow in the next few months.

Honors and Awards: None

Publications: None

Serial No. NDB (CF) - 68 E 1603
1. Collaborative & Field Research
2. Epidemiology Branch
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Familial patterns of convulsive disorders during the first year of life

Previous Serial No.: None

Principal Investigator: Robert E. Markush, M.D., M.P.H.

Other Investigator: None

Cooperating Unit: Perinatal Research Branch, C&FR, NINDB

Man Years:

Total:	1/12
Professional:	1/24
Other:	1/24

Project Description:

Objectives: The objective of this study is to determine the degree to which convulsive disorders may be genetically determined.

Methods employed: Data collected in the Perinatal Research Project are being analyzed to determine whether the immediate relatives of infants with convulsive disorders have a greater prevalence of convulsive disorders than the immediate relatives of nonconvulsive infants.

Major findings: None

Significance to biomedical research and the program of the Institute: Determination of the degree to which epilepsy or convulsive disorders are familial should have an important influence on methods for control and prevention of the disease, and should give additional information on its etiology.

Proposed course: Tables have been designed and requested from the Perinatal Research Branch. It is anticipated that they will be received before July and a final publication prepared by the end of 1968.

Honors and Awards: None

Publications: None

Serial No. NDB (CF) - 68 E 1604
1. Collaborative & Field Research
2. Epidemiology Branch
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Oral contraception and US mortality rates

Previous Serial No.: None

Principal Investigators: Robert E. Markush, M.D., M.P.H.
Daniel G. Seigel, M.D.
NICHHD

Other Investigators: None

Cooperating Unit: National Institute of Child Health and Human Development

Man Years:

Total:	1/12
Professional:	1/24
Other:	1/24

Project Description:

Objectives: To determine whether oral contraceptives have had a detectable effect upon mortality rates among women in the US, and to determine which diagnostic categories may have been affected.

Methods employed: Only mortality data already available are being used. The data are obtained from the National Office of Vital Statistics. Much of the data is available in unpublished form. Mortality trends are being analyzed for specific diagnoses and specific age and sex groups. Differences in the trends between males and females, and between females within the child-bearing ages and outside the child-bearing ages, will be noted and interpreted in light of the usage pattern of oral contraceptives.

Major findings: None

Significance to biomedical research and the program of the Institute: The use of available mortality data is not a strong method for evaluating the influence of oral contraceptives upon mortality. Positive findings, however, may suggest the need for more definitive studies. Because oral contraception is so widely used, it is important to determine its safety and its effect upon health. Among the side effects suspected of association with oral contraceptives are a series of thrombo-embolic phenomena of which cerebral thrombosis and pulmonary embolism are perhaps the most serious. Epidemiologic

studies already have indicated wide variation among populations in mortality from thrombo-embolic disease. It is, therefore, possible that different populations may have different reactions to the use of oral contraception. Although a moderate amount of data are available on the effect of oral contraceptives in England, data for the US are presently lacking.

Proposed course: Most of the unpublished data have already been obtained. These are currently being analyzed.

Honors and Awards: None

Publications: None

Serial No. NDB (CF) - 68 E 1605
1. Collaborative & Field Research
2. Epidemiology Branch
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Parkinsonism and skin pigmentation

Previous Serial No.: None

Principal Investigators: Robert E. Markush, M.D., M.P.H.
R. Michael Scott, M.D.
John L. S. Holloman, Jr., M.D.
New York City

Other Investigators: Jacob A. Brody, M.D.

Cooperating Unit: None

Man Years

Total:	1/12
Professional:	1/24
Other:	1/24

Project Description:

Objectives: The objective of this study is to verify a lower prevalence of parkinsonism among people with greater amounts of skin melanin.

Methods employed: It is planned to mail a questionnaire requesting information on the occurrence of Parkinson's Disease, and on degree of skin pigmentation to a sample of American physicians. Because of the delicacy of the questions on skin pigment, major efforts are being made to determine through pilot tests the acceptibility of such a project.

Major findings: None

Significance to biomedical research and the program of the Institute: Since parkinsonism is thought to be a disease involving pigmented regions of the brain, the finding of a lower prevalence among pigmented people would provide some further indication that the disease involves some disorder in pigment metabolism. Such information may be used either in developing treatment, methods of prevention, or in looking for other factors in the etiology of parkinsonism.

Proposed course: As soon as the Bureau of the Budget clearance is received this study will begin.

Honors and Awards: None

Publications: None

Serial No. NDB (CF) - 68 E 1606
1. Collaborative & Field Research
2. Epidemiology Branch
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Birth weight and economic status among Negros

Previous Serial No.: None

Principal Investigator: Robert E. Markush, M.D., M.P.H.

Other Investigator: Jacob A. Brody, M.D.
Elaine Lewis, R.N.

Cooperating Units: Freedmen's Hospital
Department of Preventive Medicine, College of Medicine
Howard University

Man Years

Total:	1/6
Professional:	1/8
Other:	1/24

Project Description:

Objectives: To determine whether the lower birth weights generally found among Negroes can be explained by their lower economic status.

Methods employed: A comparison of birth weights will be made between children born to private and nonprivate patients at Freedmen's Hospital.

Major findings: None

Significance to biomedical research and the program of the Institute: Freedmen's Hospital contains a larger proportion of middle income Negroes than is generally available. Should it be found that lower birth weights among Negroes are primarily the result of economic factors, any attempt to increase Negro birth weights would need to be directed against these economic, not genetic, factors. Any influence of lower birth weight on the incidence of neurological disorders would then be understood as an economic one.

Proposed course: Data on birth weights and economic status have been obtained from Freedmen's Hospital. Coding should be completed by the end of April and a final report available by the fall.

Honors and Awards: None

Publications: None

Serial No. NDB (CF) - 68 E 1607
1. Collaborative & Field Research
2. Epidemiology Branch
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Hypertension and strokes among telephone workmen

Previous Serial No.: None

Principal Investigators: Robert E. Markush, M.D., M.P.H.
George Comstock, M.D.
Johns Hopkins University School of Hygiene and Public Health Training Center for Public Health Research

Other Investigators: None

Cooperating Unit: Johns Hopkins University School of Hygiene and Public Health Training center for Public Health Research, Hagerstown, Maryland
New York Telephone Company

Man Years

Total:	1/6
Professional:	1/12
Other:	1/12

Project Description:

Objectives: To determine the relationship between blood pressure level and the subsequent development of stroke and myocardial infarction.

Methods employed: In 1963, about 1,500 telephone workers were examined. Examination included EKG, blood pressure, and interview for cardiorespiratory symptoms and cigarette smoking. These same men are being examined in 1968; in addition, their health records are being reviewed to determine rates and causes of illness and death.

Major findings: None

Significance to biomedical research and the program of the Institute: Determination of the role of hypertension, smoking, heart disease and other factors in subsequent strokes should help in understanding the etiology and prevention of this major cause of death.

Proposed course: The final follow-up examinations should be completed during the summer and analyses completed in 1969.

Honors and Awards: None

Publications: None

Serial No. NDB (CF) - 68 E 1608
1. Collaborative & Field Research
2. Epidemiology Branch
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Evaluation of the importance of common neurological conditions to mortality

Previous Serial No.: None

Principal Investigator: Robert E. Markush, M.D., M.P.H.

Other Investigator: None

Cooperating Unit: Johns Hopkins School of Hygiene and Public Health
Training Center for Public Health Research
Hagerstown, Maryland

Man Years

Total:	1/12
Professional:	1/12
Other:	0

Project Description:

Objectives: The objective to this study is to determine the true association with mortality of neurological conditions independently from diagnoses collected from death certificates.

Methods employed: A method has been developed to measure the statistical association with mortality for any disease or factor, without use of death certificate data. The method requires data on prevalence of conditions in life and at death. Prevalence in life has been determined through epidemiologic surveys; prevalence at death can be determined through several techniques, one of which has been applied in a pilot study of 507 deaths. By appending a brief disease check list to death certificates in Washington County, Maryland, more definitive data will be collected for a specific community.

Major findings: Pilot study data have suggested that strokes are somewhat more significant as a cause of death than indicated by underlying cause statistics, that myocardial infarction is considerably overestimated by the underlying cause statistics, and that hypertension may be considerably more important.

Significance to biomedical research and the program of the Institute: More accurate measurement of the effect of conditions on community mortality

should provide a powerful epidemiologic tool for determining the distributions of the more common neurological conditions, particularly those which rarely appear on death certificates.

Proposed course: It is planned to begin collection of data late in 1968. After data have been collected for one year, the first report will be prepared.

Honors and Awards: None

Publications: Markush, R.E. and Seigel, D.G.: Prevalence at Death. I. A new method for deriving death rates for specific diseases. Amer. J. Pub. Health 58:544-447 (March) 1968.

Seigel, D.G. and Markush, R.E.: Prevalence at Death. II. Methodological considerations for use in mortality studies. Amer. J. Pub. Health (in press).

Serial No. NDB (CF) - 68 E 1609
1. Collaborative & Field Research
2. Epidemiology Branch
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Prevalence of autopsy-determined vascular disease of heart and brain among medicolegal deaths in Dade County, Florida

Previous Serial No.: None

Principal Investigator: Robert E. Markush, M.D., M.P.H.

Other Investigator: John Feegel, M.D.
Medical Examiner

Cooperating Units: Dade County Medical Examiner's Office, Florida
Injury Control Program, National Center for Urban and Industrial Health, BDPEC, PHS, DHEW

Man Years

Total:	1/12
Professional:	1/24
Other:	1/24

Project Description:

Objectives: (1) To determine the prevalence of vascular disease of the heart and brain in accidental homicidal, and suicidal deaths over age 35; (2) to determine how the prevalence of vascular disease in the brain relates to vascular disease in the heart; and (3) to determine whether the degree to which the presence of vascular diseases of the heart and of the brain were associated with the manner of violent death.

Methods employed: A forensic pathologist has conducted or reviewed autopsies of all suicides, homicides, and motor vehicle deaths occurring in Dade County during July 1958 through June 1967. Findings pertaining to trauma, and other specific pathology in the lungs, heart, aorta, and brain, have been recorded in a standardized manner. The data will be processed and analyzed to meet the objectives specified.

Major findings: None

Significance to biomedical research and the program of the Institute: Because there is no way to measure atherosclerosis in living populations, resort must be made to autopsy populations to determine its prevalence. These populations are usually nonrepresentative because of selective factors

that lead to performance of autopsies on decedents. Although violent deaths are also selective and cannot represent the community's population, in many communities the fact that most violent deaths can be autopsied provides a potential means of comparing the prevalence of atherosclerosis in different populations if comparable methods are used. The first object of this study is therefore the demonstration of standardized methodology and the results of its application.

Vascular disease of the heart and brain have different population distributions, and it should be useful in determining why this occurs to compare their distributions within this study's subgroups.

The role that vascular lesions of the heart and brain may play in traumatic deaths, particularly motor vehicle deaths, has practical importance through the possibility of preventive programs. Comparing the prevalence of vascular disease in motor vehicle deaths who suffered potentially fatal injuries with their prevalence among suicide and homicide deaths of comparable ages and sexes may provide unique insight into whether vascular disease increases the risk of motor vehicle death.

Proposed course: All data collection has been completed and coding should be completed in June. A final report should be available in 1969.

Honors and Awards: None

Publications: None

Serial No. NDB (CF) - 68 E 1610
1. Collaborative & Field Research
2. Epidemiology Branch
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: National chronic respiratory mortality study

Previous Serial No.: None (Initiated in the National Heart Institute in 1961.)

Principal Investigator: Robert E. Markush, M.D., M.P.H.

Other Investigators: None

Cooperating Units: None

Man Years

Total:	1/12
Professional:	1/12
Other:	0

Project Description:

Objectives: To evaluate the effect of chronic respiratory disease upon US mortality.

Methods employed: Data on presence and severity of chronic respiratory disease in decedents have been collected by mail from about 3,000 certifiers of US deaths.

Major findings: The contribution of these diseases to US mortality is considerably more than published mortality statistics suggest.

Significance to biomedical research and the program of the Institute: The importance of these diseases to public health suggests that greater efforts should be made to control and understand them. Furthermore, published mortality statistics probably have no value in epidemiologic studies of chronic respiratory disease.

Proposed course: All tabulations have been completed and the final paper in the series should be complete by the end of 1968.

Honors and Awards: None

Publications: Markush, R.E.: National chronic respiratory disease mortality study. I. Prevalence and severity at death of chronic respiratory diseases in the US, 1963. J. Chron. Dis. (in press).

Markush, R.E.: National chronic respiratory disease mortality study. II. Mortality associated with persistent cough and phlegm in the US, 1963. (in preparation).

Serial No. NDB (CF) - 68 E 1611
1. Collaborative & Field Research
2. Epidemiology Branch
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Motor vehicle accidents in the US (1906-1964) - mortality related to age group

Previous Serial No.: None

Principal Investigator: Robert E. Markush, M.D., M.P.H.

Other Investigators: John Clark
Injury Control Program
Rhona Leibel
Injury Control Program
Carolyn Adams
Injury Control Program
Ben Ryterband
Injury Control Program

Cooperating Unit: Injury Control Program, National Center for Urban and Industrial Health, BDPEC, PHS, DHEW

May Years

Total:	1/12
Professional:	1/24
Other:	1/24

Project Description:

Objectives: To investigate the trends in motor vehicle mortality specific for age.

Methods employed: Published and unpublished US mortality rates since 1906 have been graphically analyzed and interpreted.

Major findings: Motor vehicle mortality since 1906 has been rising for those under age one and those 15-24; most other age groups have shown declines, particularly the elderly groups. It is hypothesized that inexperience, concern for self-preservation, changes in traffic regulations and road and vehicle design, increased exposure, lower ability of the elderly to adjust to hazards, and improved medical care are among the factors responsible for the age-specific trends.

Significance to biomedical research and the program of the Institute: Analysis of mortality trends has suggested potentially valuable areas for

further research in the prevention of an extremely important public health problem. New hypotheses for causation and prevention of motor vehicle deaths must be consistent with post age-specific experience.

Proposed course: A second paper is planned comparing age-sex specific motor vehicle mortality trends with those for suicide.

Honors and Awards: None

Publications: Markush, R.E., Clark, J.,Leible, R., Adams, C., and Ryterband, B.: Motor vehicle accidents in the US (1906-1964). JAMA 203:88-94 (Jan.) 1968.

Serial No. NDB (CF) - 68 E 1612
1. Collaborative & Field Research
2. Epidemiology Branch
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Studies in epidemiologic survey methods

Previous Serial No.: None

Principal Investigators: Robert E. Markush, M.D., M.P.H.
Daniel G. Seigel, M.D.
NICHHD

Other Investigators: None

Cooperating Unit: National Institute of Child Health and Human Development, NIH

Man Years

Total:	1/12
Professional:	1/12
Other:	0

Project Description:

Objectives: To determine the influence of nonresponse on the results of epidemiologic surveys.

Methods employed: Nonrespondents to a mailed epidemiologic form were requeried. The results after requery were compared with the original results.

Major findings: Questions which yielded a greater proportion of positive responses had higher response rates. Persons whose responses eventually were negative to a given question were less likely to respond than persons whose responses were positive. The bias resulting from nonresponse was at a maximum for questions that were intermediate in their proportion positive.

Significance to biomedical research and the program of the Institute:

Proposed course: Study completed.

Honors and Awards: None

Publications: Seigel, D.G. and Markush, R.E.: The interpretation of incomplete responses to a mailed epidemiological inquiry. Arch. Environ. Health, (in press).

Serial No. NDB (CF) - 68 E 1613
1. Collaborative & Field Research
2. Epidemiology Branch
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Osteoporosis, fractures, and ethnic group in Jerusalem, Israel

Previous Serial No.: None

Principal Investigators: Robert E. Markush, M.D., M.P.H.
Jacob Menczel, M.D.
Hadassah Medical Organization
Myer Makin, M.D.
Hadassah Medical Organization
Gordon Robin, M.D.
Hadassah Medical Organization
Donald G. Whdeon, M.D.
NIAMD

Other Investigators: None

Cooperating Units: Hadassah Medical Organization, Jerusalem, Israel
National Institute of Arthritis and Metabolic Diseases, NIH
Injury Control Program, National Center for Urban and Industrial Health, BDPEC, PHS, DHEW

Man Years

Total:	1/12
Professional:	1/12
Other:	0

Project Description:

Objectives: To determine how the prevalence of osteroporosis and the incidence of fractures relates to ethnic group, diet, and other environmental factors; and to determine which measures of osteroporsis relate most closely to fracture incidence.

Methods employed: A sample of the Jerusalem population is being examined for osteoporosis and followed over five years for fracture incidence.

Major findings: None.

Significnace to biomedical research and the program of the Institute: Determination of factors related to occurrence of osteoporosis should help in their prevention. Determination of measures capable of indicating risk of future fracture should help both in the understanding and in the prevention of fractures.

Proposed course: A first report should be completed in 1968. Arrangements are being made with NIAMD to incorporate a dietary history into the study.

Honors and Awards: None

Publications: None

Serial No.: NDB (CF) - 68 E 1614
1. Collaborative & Field Research
2. Epidemiology Branch
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: The effect of seat belts in government motor vehicles

Previous Serial No.: None

Principal Investigator: Robert E. Markush, M.D., M.P.H.

Other Investigators: None

Cooperating Unit: Injury Control Program, National Center for Urban and Industrial Health, BDPEV, PH, DHEW

May Years

Total:	1/24
Professional:	1/24
Other:	0

Project Description:

Objectives: To determine whether the installation of seat belts in government vehicles has been associated with a change in motor vehicle accident mortality rates.

Methods employed: A survey of government agencies was conducted to determine the timing and extent of seat belt installation. Accident records are to be correlated with the seat belt installation data.

Major findings: None

Significance to biomedical research and the program of the Institute: Although the method is unlikely to show an effect of the seat belts, since it is suspected that available belts have generally not been used, the demonstration of the lack of an effect should justify further efforts in either getting belts used or in determining why they have not been effective.

Proposed course: Temporarily suspended.

Honors and Awards: None

Publications: None

Serial No. NDB (CF) - 68 E 1615
1. Collaborative & Field Research
2. Epidemiology Branch
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Pilot study on viral antibodies in acute iridocyclytis

Previous Serial Number: None

Principal Investigators: Richard E. Goldberg, M.D.
Frank H. Reuling, M.D.

Other Investigators: John L. Sever, M.D.
Perinatal Branch, NINDB
J. Theodore Schwartz, M.D.

Cooperating Units: Laboratory of Infectious Diseases, PRB, NINDB

Man Years:

Total:	1/8
Professional:	1/8
Other:	0

Project Description:

Objectives: To study the relationship between acute iridocyclytis and serologic evidence of previous or coexisting viral infection.

Methods employed: A series of cases experiencing first episode of acute iridocyclytis will be identified. Each patient will be matched with a control subject on the basis of age, race, sex and area of residence. Blood specimens for viral antibody determinations will be drawn on each case at the time of diagnosis and again 4 weeks later. Similar specimens will be obtained on the matched comparison group. Complement fixation studies will be undertaken with a series of 40 virus antigens. Antibody response among the case and control group will be compared for the initial specimens and for change in antibody level after 4 weeks.

This pilot study is being designed to obtain preliminary data on the frequency of selected antibodies among the study and comparison groups and to appraise the logistics related to acquisition of adequate specimens and clinical documentation for case and controls. The pilot phase will comprise a series of 25 cases and their comparison subjects.

It is proposed that patients be brought into the study through ascertainment in outpatient departments of Ophthalmology at Washington Hospital and Wilmer Insititue.

Major findings: None as yet.

Significance to biomedical research and the program of the Institute: The cause of acute iridocyclytis remains an enigma. Through this method of study it may be possible to identify viral agents worthy of more detailed study as possible causes of iridocyclytis.

Proposed course: The project is continuing.

Honors and Awards: None

Publications: None

Serial No. NDB (CF) - 68 E 1616
1. Collaborative & Field Research
2. Epidemiology Branch
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Comparison of glaucoma suspects identified by different methods of tonometry

Previous Serial Number: None

Principal Investigator: J. Theodore Schwartz, M.D.

Other Investigators: None

Cooperating Units: None

Man Years:

Total	1/4
Professional:	1/8
Other:	1/8

Project Description:

Objectives: To determine the influence of variation in the method of tonometry on the selection of glaucoma suspects.

Methods employed: Data obtained in community-wide surveys previously undertaken by this Section were reanalyzed to identify and compare those individuals who were selected as positive screenees by different tonometric methods. Data from previous surveys at Nesquehoning, Penn. and Colorado River Reservation, Arizona were used in this study. In these surveys intraocular pressure of each examinee was measured by 3 different methods: Goldmann applanation in the sitting position, Goldmann applanation in the supine recumbent position, and Schiotz in the sitting position.

Major findings: At the critical screening level of 21 mm hg, slightly fewer than 1/3 of those individuals who were positive by any method were positive by all 3 methods. With regard to the more commonly employed method of tonometry, that is, Schiotz measurements and Goldmann applanation measurements taken in the sitting position, only half of the persons who were identified as positive screenees by either method were so classified by both. The extent of agreement in identifying positive screenees at the critical screening level of 25 mm hg was no better.

Significance to biomedical research and the program of the Institute: The extent of agreement among these tonometric procedures in selecting positive screenees was limited. The findings suggest the need for further

investigation of the efficiency of tonometric screening for glaucoma.

Proposed course: This project is continuing.

Honors and Awards: None

Publications: Schwartz, J.T.: Vagary in tonometric screening. American Journal of Ophthalmology 64: (July) 1967.

Serial No. NDB (CF) - 68 E 1617
1. Collaborative & Field Research
2. Epidemiology Branch
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Television Ophthalmoscopy

Previous Serial No.: None

Principal Investigators: J. Theodore Schwartz, M.D.
C. A. Caceres, M.D.
NCCDC
R. L. Dallow, M.D.
NCCDC

Other Investigators: None

Cooperating Unit: Medical Systems Development Laboratory
Heart Disease and Stroke Control Program
National Center for Chronic Disease Control

Man Years:

Total:	1/2
Professional:	1/2
Other:	0

Project Description:

Objectives: To coordinate the development of an instrumentation system utilizing television ophthalmoscopy and electronic data processing.

Methods employed: The Section on Ophthalmic Field and Developmental Research and the Medical Systems Development Laboratory have entered into an agreement to undertake collaborative development of a practical instrumentation system utilizing television ophthalmoscopy and electronic data processing. Under this agreement the MSDL will (a) conduct a detailed systems analysis of the potential applications of TVO; (b) prepare, on the basis of the systems analysis, recommendations for optimal applications of a system of TVO and automatic data processing; (c) prepare a detailed system development plan in terms of cost and development time, and, following NINDB review and approval, (d) implement recommended method of development including design, assembly and testing of equipment.

Major findings: Applications of TVO have been reviewed and an order of developmental priority has been established. Pending approval and funding, assembly of instrumentation, clinical trials, data acquisition and programing for automatic processing of the electronic signals will follow.

Significance to biomedical research and the program of the Institute: Measurements such as circulation time, ophthalmodynamometry and glaucomatous cupping of the optic nerve head will be attempted. With successful development, applications of this modality hold promising value in mass screening programs, basic research and clinical practice.

Proposed course: This project is continuing.

Honors and Awards: None

Publications: Williams, G.R. and Schwartz, J.T. (eds.): Television Ophthalmoscopy (Proceedings of NINDB Workshop, 1965). PHS Pub. No. 1490, U.S. Gov't Printing Office, 1966.

ANNUAL REPORT
For Period July 1, 1967 through June 30, 1968
Perinatal Research Branch
National Institute of Neurological
Diseases and Blindness
National Institutes of Health

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ANNUAL REPORT
For Period July 1, 1967 through June 30, 1968
Perinatal Research Branch
National Institute of Neurological
Diseases and Blindness
National Institutes of Health

SUMMARY OF SCIENTIFIC OR PROFESSIONAL ACCOMPLISHMENTS

This year has witnessed a consolidation of the program of the Perinatal Research Branch starting with the change from grant support for the participating institutions in the Perinatal Collaborative Study to contract support as of July 1, 1967. The transition was accomplished without any major difficulties, and has resulted in a streamlining of the decision-making process, the identification of a focal authority responsible for the Perinatal Collaborative Project.

These administrative and organizational changes were accomplished with the advice and assistance of the Perinatal Research Committee whose role continues to be strengthened.

There were developed during the past year also, procedures to monitor data collection more closely than before and to routinely test-retest, through an inter-institutional rotation schedule, a five percent sample of children from the Collaborative Project at three, four, seven and eight years of age. In addition, test-retest procedures are being implemented within individual institutions to monitor comparability between the different examiners of our Collaborating Institutions.

Obviously the follow-up of children from the Collaborative Study is preoccupied with the problems of retaining with minimal loss the children from this program through the final examination at eight years. Retention rates have been up from 75 percent at seven years during the previous year to 80 percent during this fiscal year. However, there are still two institutions where serious problems have arisen because of a disproportionately large loss of children for the later examinations. Methods are currently under development through contact with various agencies to hopefully improve the identification of children lost to the Study in order to further reduce attrition. It is obvious that these problems will continue to require attention during the coming years.

Review editing and coding and key punching of data collection forms which are received from the Collaborating Institutions by the appropriate units of the Perinatal Research Branch represents no major problem and is up to date in most areas.

Up-dating of data files has been accelerated and is done more frequently in an effort to have a most complete file available at all times for data review and analysis. To improve efficiency and reduce turnaround time of request requiring data retrieval, serious consideration has been given to the creation of summary tapes and separate condensed data files representing sets of information most likely needed for various analyses.

The development of a more systematic approach to the analysis of the large amount of data collected on pregnant women and their children by this program has received serious attention but has proven to be a very difficult problem. The inter-disciplinary collaborative nature of the Perinatal Research Program is an effort that has only been possible through the participation of large numbers of professional individuals from many different medical and paramedical disciplines in our participating institutions and the Perinatal Research Branch. A systematic plan for data analysis has to incorporate in it the interest and needs of these participating professionals in order to retain their interest as well as take advantage of their knowledge of the information available. Coupled with this is the interest of groups of people outside the framework of the Collaborative Study from other institutes of the NIH, other agencies within the Department of HEW, and from private and university groups, to get answers to specific questions where often the data of the Collaborative Project represents the only source. It is not at all difficult to exhaust completely the resources for Study development, data retrieval and analysis of PRB by responding to requests for data from these various groups.

The possible solution to this problem, which is currently under consideration, is through further strengthening of the professional staff of the Perinatal Research Branch and the participation of a few select highly expert and competent senior professionals in the disciplines contributing to this program from the outside. In the selection of such experts, great care should be exercised to identify people with a strong background in research methodology design and in the handling of masses of information. We are contemplating some kind of a formula whereby approximately two-thirds of the resources for data retrieval and data analysis of the Perinatal Research Branch will be devoted to the systematic analysis of information from the Perinatal Research Program according to a data analysis plan with the remainder of the resources being made available to pursue requests from individuals from within and without the Collaborative Project and the occasional original idea that is generated and brought to our attention.

During this past year about 60 percent of our resources in data retrieval were taken up by the development of information for the Ad Hoc Statistical Committee which continues a searching review of the data of the Perinatal Research Program.

In addition a considerable portion of staff time was devoted to the activities of this Ad Hoc Review group. For those of us fortunate to interact closely with the Committee, it was certainly a very gratifying experience and the review of this Committee may well serve as a model for future application.

There are still unmet needs in the Perinatal Research Branch.

Foremost, is the need to recruit a senior epidemiologist to assume a key responsibility in the further evaluation and analysis of the data of the Perinatal Research Program. Also, a senior psychologist is still to be recruited.

We acknowledge gratefully the support which the Perinatal Research Branch has received from the Office of Biometry of the NINDB, through the assignment of

a systems analyst, and several programmers to provide the necessary competence for data processing and data retrieval. The service these individuals have provided has become more effective through the year and with the creation of summary tapes, condensed data files and better prepackaged programs, further increase in efficiency is expected. There is still, however, a serious problem in meeting the statistical needs for the direction of the program, the evaluation of quality control procedures established and others to be devised, and for the planning and execution of data analysis. While it is acknowledged that a considerable shortage exists regarding the availability of senior statisticians, it is imperative that at least one senior statistician be assigned on a full-time basis as soon as possible to the Perinatal Research Program, who could then be supplemented with junior statisticians working under his direction.

PROGRAM ACCOMPLISHMENTS:

Despite the preoccupation during this fiscal year with the services to be provided through data retrieval to the evaluation of the adequacy of statistical base of the data of the Collaborative Study by the Ad Hoc Statistical Committee, considerable progress has been made in the analysis of specific relationships of prenatal characteristics to pregnancy outcome. These are reflected in the reports of individual sections and are only highlighted by the following summary.

Of considerable importance are observations indicating an effect on intelligence among children of mothers whose pregnancy was complicated by diabetes. Significant depression of intelligence scores was noted among the offspring of diabetic mothers as compared to controls, and was found to be principally associated with diabetes in pregnancy complicated by acetonuria. Subsequent analysis of intelligence scores of children whose mothers had acetonuria without diabetes has confirmed this association between acetonuria and lower I.Q. It is in this context also significant to note that the frequency of acetonuria without diabetes was about four times as high among the indigent population of the Study as compared to others, and suggests quite strongly that borderline nutritional states complicated by various illnesses such as severe hyperemesis gravidarum may alter maternal homeostasis sufficiently to result in acetonuria. This problem will be vigorously pursued at this point in view of its obvious important significance as a factor in mental retardation.

Other factors found to be related to I.Q. depression in childhood have been identified. These are hypertension associated with proteinuria, proteinuria without hypertension or evidence of toxemia, and intrauterine growth retardation.

Another observation of potentially considerable significance was the analysis of data relating weight gain in pregnancy to birthweight of offspring. There is a positive correlation between weight gain in pregnancy and the birthweight of the child which we have consistently demonstrated. This relationship has been confirmed using data unrelated to the Collaborative Study, collected in one institution prior to the onset of the Study.

Additional evidence has accumulated suggesting strongly that spastic diplegia may be the result of intracranial hemorrhage possibly following thrombosis of a major cerebral vessel and occurring during the first few days of life. Work in progress suggests that the occurrence of this event conceivably can be forecast on the basis of simple laboratory monitoring.

A. SECTION ON OBSTETRICS

Report for the Period July 1, 1967 through June 30, 1968

I. SUMMARY OF SCIENTIFIC OR PROFESSIONAL ACCOMPLISHMENTS

During the period of time covered by the present report, the professional staff of the Section was requested to cooperate in different types of large-scale operations of editing, coding, case reviews and obstetric data reviews. These activities have contributed to complete the obstetric data file, but they have left little time for the staff to proceed with the analysis of the data as outlined in the annual report for 1966/67.

The following studies have been completed:

Mothers of mongoloids in the Collaborative Project

Obstetric and clinical factors characterizing the mothers of 62 mongoloids identified in a population of 55,932 gravidae in the Study have been analyzed in comparison with a control group matched for age, race, hospital and date of the last menstrual period. It was found that the incidence of mongolism in whites and Negroes is nearly equal. The distribution of the maternal ages is bimodal, but there are more white mothers in the younger age groups and more Negroes in the older age groups. No differences were found in parity, pregnancy-free interval, number of prior abortions or past medical history between the study and the control groups. Both birthweight and duration of pregnancy are slightly less for the study group than for the controls. There were more male than female mongoloid infants. A very similar drug and x-ray experience in the study and the control groups has been noted. (This paper by Dr. J. Marmol and co-authors will be published in the American Journal of Obstetrics and Gynecology.)

Respiratory distress syndrome in babies born to mothers receiving acetazolamide during labor and delivery

Depression of carbonic anhydrase activity has been reported in newborns with R.D.S. Since acetazolamide acts by depression of that enzyme, it was thought that maternal ingestion of acetazolamide during labor might result in an increased rate of R.D.S. in their babies. A review of approximately 300 cases reporting ingestion of acetazolamide during labor has produced negative results. (This paper by Dr. A. L. Scriggins and co-authors will be submitted as a letter to the editor of the New England Journal of Medicine.)

Prenatal drugs

To analyze the reporting of prenatal drugs in the core population of the Collaborative Project, a classification of all drugs coded in the Study was devised. A computer program has been designed to retrieve all prenatal drugs by classification, race, hospital, trimester of reporting

and trimester of registration of the mother for prenatal care. (This study by Dr. A. L. Scriggins and co-authors is in the computer programming stage.)

Oxytocin-induced water intoxication

This is a case report on a maternal death in an uncomplicated, incomplete abortion due to acute water intoxication following oxytocin treatment, with a review of the literature. It has been established that oxytocin may cause water retention and, consequently, electrolyte imbalance. This is the first reported maternal death due to oxytocin water intoxication. (This paper by Dr. A. A. Lilien has been accepted for publication in Obstetrics and Gynecology.)

Term intrapartum fetal death

The objectives of this study are to characterize the maternal, fetal and obstetric factors associated with the death of the term fetus during labor. From a base population of 55,000 deliveries, 450 term fetal-neonatal deaths were reviewed and 88 term intrapartum deaths were identified. It was found that nearly in all cases of fetal death during labor, definite abnormal clinical findings can be documented in the Study record. These clinical findings seem to be more relevant to the etiology of intrapartum fetal death than the diagnoses based on post-mortem pathologic findings. (This paper by Dr. A. A. Lilien will be submitted for publication in the American Journal of Obstetrics and Gynecology.)

The length of the premenstrual phase by age of women

For this study 12,751 menstrual cycles and basal body temperature curves contributed by 546 healthy women have been analyzed. They cover the whole reproductive period from menarche to menopause. Following menarche, 45 percent of the menstrual cycles are anovulatory. The rate of the anovulatory cycles constantly decreases during the period of adolescence, and it reaches a minimum at age 23. Between 23 and 44 years of age, an average of only 2 percent of the menstrual cycles are anovulatory. At age 45 years, the rate of anovulatory cycles increases steadily toward the menopause. In addition to the anovulatory cycles, menstrual cycles with short premenstrual phases of 3 to 10 days' duration ("insufficient corpus luteum phase") can be identified by this method. These cycles with short premenstrual phases were observed in about 40 percent of the menstrual cycles during adolescence, but they decreased to only 20 percent during maturity. This rate did not increase during the preclimacteric phase. The importance of these findings relative to human fertility and sterility was discussed. (This paper by Dr. R. F. Vollman was presented at the Fifth World Congress on Fertility and Sterility in Stockholm and published in Excerpta Medica International Congress Series No. 133.)

Distribution of fertile and sterile coitus by days of the menstrual cycle

Over the past 30 years calendar records have been collected on the menstrual cycle, basal body temperature, and dates of coitus in a group of healthy,

fertile women. These data have been analyzed in respect to the occurrence of conceptions by day of the menstrual cycle and in relation to the rise of the basal body temperature. Conceptions were observed after single matings between days 5 and 59 of the menstrual cycle, with a mode of conceptions for days 14 and 15 indicating that fertile days in women cannot be specified precisely to the day of the menstrual cycle when the point of reference is the first day of the cycle. When the point of reference is the rise of the basal body temperature, conceptions occurred on the first day of the temperature rise and on the nine preceding days. Most conceptions resulted from coitus on the first day before the rise of the temperature. Even on this optimal day, the conception rate (conceptions/exposures) does not reach 20 percent. This is the first time that a coitus-conception rate has been established in women. The astonishing low rate requires further research into the processes of ovulation, fertilization and implantation in the human. (This paper was requested by the WHO Research Group on Human Reproduction and will be published in Research in Mammalian Reproduction.)

Menstruation and ovulation in the monkey

The late Dr. Carl G. Hartman has left a large file of observations on ovulation, conception, outcome and duration of pregnancy in the monkey that has never been systematically analyzed. At Dr. Hartman's request and with the cooperation of Dr. J. D. Ebert, Director of the Department of Embryology, Carnegie Institution of Washington, these data have been abstracted from the original protocols and have been analyzed for publication. (This paper by Dr. R. F. Vollman and co-authors will be presented at the International Congress of Primatology and published in Contributions to Embryology.)

II. PROBLEMS

The systematic analysis of the obstetric data now available in the complete data file requires the appointment of at least one additional research-oriented obstetrician. Former obstetric coordinators from collaborating institutions are willing to join the Section temporarily on specific research assignments.

III. PROPOSED FUTURE OBJECTIVES

A. Systematic description and analysis of the obstetric data at large.

The Section has outlined the basic obstetric variables and their classification for a general description of the gravidae in the Study. As soon as all obstetric data are available on tape, a series of frequency distributions of important obstetric variables will be requested to describe the basic characteristics of the gravidae in the Study.

B. Specific studies relating obstetric and medical factors during pregnancy to different types of outcome.

Two interrelated studies that have been carried over will be programmed: a) evaluation of gynecologic versus chronologic age of the gravida in relation to birth weight and duration of pregnancy and b) in relation to fetal death.

In addition, a number of studies are planned involving small numbers of cases (certain drugs, elective obstetric procedures, laboratory findings). The data will be directly abstracted from the original case record by the trained auxiliary personnel in the Section.

IV. MISCELLANEOUS

On request of the Lilienfeld Committee, Dr. J. Marmol made an extensive research of the obstetric literature on incidence figures of 47 specified obstetric variables.

Mrs. A. Litz compiled a history of the development and the changes in content of all obstetric forms and editing manuals.

The Section was host to Dr. Kenneth I. E. MacLeod who lectured on the classification of malformations and to Dr. Elizabeth Ramsey who presented an unusual series of cine-radiographic motion pictures on the maternal and fetal circulation in the monkey at different stages of pregnancy.

Members of the Section presented papers on intrapartum fetal death, on mothers of mongoloids, and on intercourse and conception rates in fertile women.

Mrs. A. Litz spoke to Graduate Public Health students, attended research seminars at the ACOG Meeting, and participated in a Family Planning Three-Day Workshop.

Dr. A. Lilien attended the Annual Meeting of the American Fertility and Sterility Association.

Dr. R. F. Vollman was invited to chair a round-table conference on oral contraceptives which is to be held at the Sixth World Congress on Fertility and Sterility. He participated in the Annual Proceedings of the Society for Gynecologic Investigation.

B. SECTION ON PEDIATRIC NEUROLOGY
Report for Period July 1, 1967 through June 30, 1968

I. SUMMARY OF SCIENTIFIC OR PROFESSIONAL ACCOMPLISHMENTS:

A. Logistics:

The one-year neurological examination has been completed on the study population. The Section is deeply involved now in collection of data on the 7-year neurologic examination. Duplicate neurologic examinations are being conducted at the various institutions to detect reproducibility and maintain uniformity of test method, called quality control.

A diagnostic summary made at the time of the 7-year examination is being completed on each case. One purpose of this instrument, form IDC-77, is to identify and describe cases with so-called minimal cerebral dysfunction, utilizing data from psychology, and speech, language and hearing.

An EEG Committee has been working on a protocol for EEG studies of a subsample of the study cohort, beginning with six institutions. Rather slow progress has been made toward a start of this study. Quality-control work has finally been accomplished; the study sample of cases and controls has been delineated fairly well; and a Study protocol has been drawn up. At a final meeting, in the near future, a study proposal will be drawn up and submitted to the Branch Chief. Problems facing EEG study are:

reproducibility of EEG interpretations,
participation of all institutions in EEG,
loss of sample,
preparation of study design proposal.

B. Product:

The study plan of the Section at present places priority on three major lines of inquiry. While the scope of two of these appears to be totally different, the manner in which they interact may be demonstrated at a later date.

The first line of inquiries centers upon maternal factors which are presumed to interfere with fetal nutrient supply.

The second centers upon the question in intrapartum cerebral trauma. This latter program is being shared with the Section on Behavioral Sciences.

The third study is concerned with the problem of spastic diplegia of cerebral palsy.

A number of studies relating to fetal nutrient supply have been generated during the past year, and the following manuscripts are about to be submitted for publication: Neuropsychologic Deficits in Children of Diabetic Mothers, The Effect of Maternal Hypertension with Proteinuria on the Neuropsychological Outcome of the Child, Neuropsychological Outcome in Children Whose Mothers Were Given Tetracycline During Pregnancy, Neuropsychologic Outcome of Children Whose Mothers Had Proteinuria During Pregnancy, and Neuropsychologic Deficits in Children Whose Mothers had Episodes of Acetonuria. Another study, supported by contract in collaboration with another institution, has been submitted for publication; Relationships of Maternal Amino Acid Blood Levels to Fetal Development.

A study of protein deprivation of pregnant mice, shared with the Section on Pathology, is well advanced. The primary objective of this study is to search for structural changes in brains of offspring of protein-deprived mice. The first steps of this project has been completed; namely, the breeding and the behavioral testing of the mice and the preparation of the brains. It should be pointed out that behavioral differences were found between protein-deprived and control groups.

Studies on intrapartum trauma include the following: a) Neuropsychologic differences between children born LOA and ROA (see Section on Behavioral Sciences' report for detail), b) relationship between pelvic and neuropsychologic measures (see Section on Behavioral Sciences), c) the occipit-posterior position and neuropsychologic outcome, and d) neurologic status of breech delivery.

The Sections on Pediatric Neurology and Behavioral Sciences, along with Dr. Caldeyro-Barcia, are committed to present a section of a symposium on physical trauma as a cause of mental retardation in October 1968, at Lincoln, Nebraska.

Investigation continues on the problem of spastic diplegia of premature, the most common type of cerebral palsy. In addition to confirming the previous finding, that spastic prematures have greater postnatal weight losses than do non-spastic prematures of comparable weight, it was found that spastic prematures had a significantly greater postnatal fall in blood hematocrit levels than do non-spastic prematures. The possibility thus is entertained that spastic diplegia of prematurity is associated with internal hemorrhage, the hemorrhage frequently being in the brain. In conjunction with the Section on Pathology, preliminary study reveals that premature infants dying early in life, who have low postnatal hematocrit levels, do indeed have intracerebral hemorrhage;

whereas, those whose hematocrit levels do not reach low levels lack hemorrhage. A systematic review of all study prematures is underway to obtain, as near as possible, the full picture and sequence of events.

II. PROBLEMS:

A. Sample maintenance is, of course, of considerable concern to the Section in obtaining a 7-year neurologic examination follow-up. Procedures of various institutions have been reviewed to see what situations are peculiar to each.

B. The possibility of tracing lost cases through various agencies has been explored.

C. The pursuit of individual studies has been seriously hampered in the past year by serious delays in data processing. It is hoped, now that data processing has been relieved of a large commitment, more rapid progress can be made. It would appear that there is much that could be done to improve communication between medical investigators and data processing personnel.

III. PROPOSED FUTURE OBJECTIVES:

One major objective is to see whether the intelligence of children can be improved by improving protein balances in the mother. The immediate thing to do would be to set up a clinical trial of supplementing diets during pregnancy. Undoubtedly, clinical trials of this sort will be started in various places. However, it is considered that it would be wiser to see if more direct measures of nutrient balance can be worked out. The work on the relationship of maternal amino-acid levels to birthweight of the child, where dietary assessment shows only a trend of a similar relationship, suggests that one might be able to measure the need for nutrient supplementation to measure the extent of nutrient inadequacy by such chemical means. An important step is to see if some amino-acid species relate more clearly to birthweight and cranial volume than others. One might postulate that the essential amino acids would be critical in determining fetal size while the non-essential ones would not. We are now prepared to do complete amino-acid studies on 75 cases in which the total amino-acid level and outcome of the child are already known. Another proposed study is to determine whether amino-acid levels differ between groups of patients upon whom we have already found differences in birthweight and intelligence. Specifically, do mothers with diabetes have lower levels of some amino acids as well as have children with lower I.Q. than their matched controls; do women with acetonuria during pregnancy have lower amino-acid levels than their matched controls, etc.? Since cases and matched controls have already been identified in the course of several previous studies, and since frozen serum samples of these patients are available, it should be possible to run the sera for

amino acids and relate these findings to the already known data. To accomplish this aim, it is proposed that the Perinatal Research Branch obtain a qualified protein chemist and establish him in a laboratory to perform his work. His investigation should not be limited strictly to the amino acids, but include peptides, peptide enzymes, and blood proteins. The future objectives of the perinatal brain trauma studies probably have been described by the Section on Behavioral Sciences. It is necessary only to point out here that these studies are concerned with the question of cerebral dominance, a classical problem in neurology, and with central problems of human brain evolution.

C. SECTION ON BEHAVIORAL SCIENCES

Report for the period July 1, 1967 through June 30, 1968

I. SUMMARY OF SCIENTIFIC OR PROFESSIONAL ACCOMPLISHMENTS

A. Research Findings

1) Children delivered in the right occiput anterior position earned significantly lower Stanford-Binet IQs at four years of age than those delivered from the left occiput anterior position despite the use of forceps. Also children delivered ROA without forceps earned a significantly lower WISC Verbal IQ at seven years of age than those delivered LOA without forceps (Willerman and Churchill).

2) Children of women coded as having borderline or contracted pelvic outlets earned significantly lower Stanford-Binet IQs at four years of age than those of women coded as having adequate pelvic outlets (Willerman and Churchill).

3) Children born of small pelvis mothers had significantly lower WISC Verbal IQs at seven years of age than those born of large pelvis mothers. Also those children of mothers with small pelves who had been delivered by forceps made significantly more errors on the Tactile Finger Recognition Test administered at seven years of age than those of large pelves mothers delivered by forceps. All children delivered by forceps made significantly more errors on the Bender-Gestalt test, given at seven years of age, than those delivered without forceps. (Willerman and Churchill)

4) Preliminary investigation shows that the relationship between the Bayley Motor score at eight months of age and the Stanford-Binet IQ at four years of age varies with the social class of the child. This study is still in progress and additional data is being retrieved. (Willerman and Sledge)

B. Data Collection

1) The Eight-Month Psychological Examination. (PS 1-5) Data collection has been completed with this protocol. Examinations on approximately 43,800 children have been received in this section, edited, coded and sent out to be transferred to punch cards.

2) The Four-Year Psychological Examination. (PS 20-25) Data has been collected with this protocol and received in the Section on approximately 25,000 children or about one-half of the total expected sample. As of March 18, 1968, all 4-year examinations, after editing, are transferred to Central Coding for coding, thus freeing time for the editing and coding of 7-year psychological examinations. As of March 31, 1968, a backlog of approximately 1800 4-year examinations was accumulated in the Section to be edited.

3) The Seven-Year Psychological Examination. About 6400 of these examinations have been received. Training sessions in editing and coding have been conducted and processing has begun.

4) The Seven-Year Psychological Examination Signs and Symptoms Checklist. (PS-39) This summary form, and a manual, covering eight broad areas of performance was devised to identify children exhibiting signs thought to be indicative of minimal cerebral dysfunction. It is based on test responses and behavior of the child at the time of the 7-year examination and contains information to be transferred to the Interdisciplinary Diagnostic Code. This form is now in use on a trial basis in all of the collaborating institutions.

5) School Follow-Up Record. This form was developed to obtain data from the schools on (1) a sample of children from each institution who have been examined at seven years of age and (2) children who had failed to appear for the seven year examinations as of July 20, 1967 and whose addresses were known. This data from the schools includes grade placement, IQs, and achievement test scores. For the first sample it is to be compared with IQs and achievement test scores from the seven year psychology battery; for the second sample it will provide some information on children who failed to report for the COLR evaluation. Preliminary analysis of the forms received show that (1) very few have been returned on children who failed to report for the seven-year battery; (2) the information returned is in many cases incomplete; e.g., no IQ test had been administered to the child in school; (3) such a wide variety of achievement tests have been administered that comparability with COLR data is doubtful; (4) an analysis of a small sample of cases (N=70) showed sugstantial agreement between "school" IQs and COLR IQs at seven years.

C. Interinstitutional Quality Control

Twenty-four quality control trials are scheduled each year in which institutions are paired, and psychologists from visiting institutions retest a yearly total of 144 children previously tested in the home institutions with the 4 and 7 year psychology batteries. These retests are observed by a psychologist from this Section who then discusses the results with all of the psychologists involved. This procedure allows for resolution of discrepancies in methods of testing, scoring and handling children as well as providing test-retest reliability coefficients for the 4 and 7 year examinations.

II. PROBLEMS

One of the major problems has been the delay involved in the retrieval of both raw data and computer feedback for data analyses. Another major problem is the acute shortage of office space for professional personnel. The recruitment of a third psychologist is also a current problem.

III. PROPOSED FUTURE OBJECTIVES

The continuation of analysis of the psychological data collected at 8 months, 4 years and 7 years, as these data are interrelated and as they are related to data collected within other disciplines. An additional psychologist and of course increased efficiency in data retrieval will facilitate this process. Future research activities will involve, in addition to data analysis of the Khanna et. al. study described in the Individual Project Reports, the following studies which are now in the planning stages.

1) A study exploring the sociological, biological and genetic characteristics of interracial matings is being designed in collaboration with the Section on Epidemiology and Genetics.

The collaborators with Dr. Willerman of our Section are Drs. Myrianthopoulos and Naylor. We have approximately 250 such matings and we are going to explore the characteristics of these mothers as well as the characteristics of their offspring.

2) Relationship of Social Class and Intelligence Level to Stability of IQ from Four to Seven Years of Age (Sledge).

3) The Contribution of the Genetic Component to Variance in Intelligence: A Comparison of Intelligence measured at Eight Months, Four Years and Seven Years among Identical Twins, Fraternal Twins, Siblings and Unrelated Children (Sledge).

IV. MISCELLANEOUS

Organizational Changes. Lee Willerman, Ph. D., was appointed as a Research Psychologist, effective August, 1967, Sarah H. Sledge, Ph. D., was appointed as Acting Head of the Section on Behavioral Sciences, effective November, 1967, Raymond H. Holden, Ed. D., has been appointed as Visiting Scientist, September 1968 through June 1969.

D. SECTION ON INFECTIOUS DISEASES
Report for period July 1, 1967 through June 30, 1968

I. SUMMARY OF SCIENTIFIC OR PROFESSIONAL ACHIEVEMENTS

LARGE-SCALE SEROLOGICAL TESTING

Three types of studies are being conducted:

Broad serological approaches to identify the viruses which are infecting the study population.

Complete serologic testing for 7,000 pregnant women for 5 antigens has been analyzed. The antigens include rubella, influenza A, herpes simplex, mumps, and cytomegalovirus. Approximately 70 women showed evidence of infection with each of these viruses during gestation. The analysis of the pregnancy outcomes for these patients and matched controls is now being prepared. The association of clinically recognized infections with pregnancy outcomes is also being analyzed in detail.

Intensive studies of important infectious agents.

The frequency of cytomegalovirus infections in pregnant women during gestation has been investigated in 2 studies. First, it has been found that 7 of 200 women tested were excreting cytomegalovirus at the time of delivery. In addition, the virus has been isolated from 3 of 500 newborns when specimens were obtained within 24 hours of life. The children of these pregnancies are being followed with matched controls to determine the possible effects of these infections.

Selected studies of pregnancies with abnormal outcomes and matched controls.

Groups of patients with congenital heart disease and malformations of the central nervous system have been identified and serologic tests have been completed for these patients along with matched controls to determine the possible influence of a variety of virus infections in relation to these outcomes.

Research on the development of antigens for use in the study of viral infections of pregnant women in the Collaborative Perinatal Research Study has resulted in the production of large quantities of 125 antigens.

STUDIES IN EXPERIMENTAL ANIMALS

Ferrets were found to develop chronic infection similar to that of man. Congenital infection appears to be limited and clearly associated with virus induced embryopathies. A number of studies utilizing ferrets have indicated that factors other than those controlled within the scope of the infection may result in a variability in pregnancy wastage which is larger than that due to the inoculation of organisms.

Pregnant monkeys inoculated with vaccine strains of rubella (HPV 77 of Gilchrist P 48) show no evidence of fetal transmission of the infection while fully virulent or field strains of the virus do transmit readily to the fetus.

Congenital cytomegalovirus infection has been studied in experimental mice. The mouse salivary gland virus infection is modified by the pregnancy state and thus appears to alter the pathogenicity of the virus.

ISOLATION OF AGENTS AND CHROMOSOME STUDIES

PPLO isolations have been made from spontaneous abortions. Further studies of the normal flora of the vagina in relation to these organisms are being extended. Chromosome studies indicate a high incidence of cytogenetic abnormalities associated with early spontaneous abortions and a lower incidence with late spontaneous abortions.

VOLUNTEER AND VACCINE AND SPECIAL STUDIES

Several studies were conducted with volunteers at the Petersburg Federal Reformatory using the Gilchrist P 48 vaccine strain. It appeared that this strain is a true vaccine strain for further clinical testing as further indicated.

VACCINE DEVELOPMENT PROGRAM

Duck adapted Gilchrist P 48 vaccine has been prepared and is being studied. In addition, sedimentable and nonsedimentable antigenic components have been studied as possible inactivated vaccine preparations.

VD PROGRAM

Cultivation of rubella virus in avian tissue cultures was accomplished through multiple passages. Hemagglutination antigen was also prepared in suspension cultures. Rubella virus was found to be cultivated in the presence of serum substitutes including human serum albumin.

MULTIPLE SCLEROSIS AND SUBACUTE SCLEROSING PANENCEPHALITIS

Serologic studies with patients with multiple sclerosis continue to show elevated measles antibody levels for the patients affected by this disease when compared to matched controls. Patients with SSPE show remarkable elevation in the serum and spinal fluid levels to measles. Siblings and parents to these patients however, do not have any elevated antibody levels. Skin testing of patients with multiple sclerosis have failed to show any elevated reactivity when measles antigens were used. Similar studies with SSPE patients are now in progress.

II. PROBLEMS

LACK OF FUNDS FOR MATERIALS NECESSARY FOR STUDIES

Because of the reduction in the research and development contract funds for virus reagents this year, it has not been possible to prepare many of the important antigens for testing. No cell pack antigens for the adeno-viruses or herpes simplex could be provided. This has resulted in a restriction of testing performed.

INSUFFICIENT PERSONNEL

We continue to be severely limited by the lack of sufficient positions for technicians, a secretary, Serum Center personnel, and statistical clerks. A minimum of six additional positions are necessary for efficient utilization of serum and antigen. This is particularly necessary because an increasing percentage of sera have demonstrated marked deterioration. Only through efficient utilization of procedures which are available will it be possible to obtain information concerning the exposure of patients to viruses and the importance of this exposure to the production of abnormal infants.

VARIABLE ANTIGENIC PREPARATIONS

It is apparent that the biological systems involved in producing the antigens are frequently not reproducible. Frequent changes in procedures, changes in tissue or special methods of concentrating antigenicity are necessary to obtain a new lot of antigenic material. In other cases anticomplementary effects must be eliminated or the antigens may have to be remade. The production of antigens requires individual research and development.

III. PROPOSED FUTURE OBJECTIVES

ADDITIONAL PERSONNEL

Every attempt will be made to obtain six new positions in Fiscal Year 1969 which are absolutely necessary for our study. Two of these positions will be for laboratory technicians for emergency testing of sera which are undergoing loss of activity; two positions will be for assistance to unpack and make available the back log of over 1 year of serum collection (160,000 vials). Two positions will be used for analysis of the back log of test data and secretarial assistance to correlate data being punched from the Obstetrical and Pediatric records.

VACCINE STUDIES - RUBELLA VIRUS

Further studies on inactivated and attenuated vaccines for rubella will be pursued. These will include animal inoculation of vaccine materials to determine antigenic potency as well as possible administration to volunteers using safety tested material.

GAMMA GLOBULIN STUDY

The efficacy of the use of gamma globulin for the prevention of rubella will be extended using titered gamma globulin in controlled studies in Honolulu, Hawaii.

EXPERIMENTAL ANIMALS

Further investigations will be conducted with experimentally infected pregnant and nonpregnant animals to provide direct information on routes of infection, pathogenesis, and possible methods of prevention of defects in the fetus due to infectious agents. Experimental animal studies will continue in pregnant monkeys obtained under contract arrangements. Viruses under study will include rubella, mumps, and cytomegalovirus.

SPECIMEN COLLECTION

Specimen collection will be expanded to include tissue samples from placentas & abortuses at the Kaiser Hospitals in California and Hawaii so that the isolation of viral agents may be utilized to confirm and extend the serological findings. Simultaneous cytogenetic studies will be performed. Special fetal specimens will be studied from patients with abortions.

NEUROLOGICAL DISEASES AND EYE DEFECTS

A laboratory for the study of defects of the central nervous system and eyes which are due to infectious agents has been developed. This laboratory is using the combined techniques of infectious diseases and fluorescent microscopy.

CYTOGENETIC STUDIES

The laboratory for cytogenetic studies will be expanded to work in conjunction with the infectious disease studies of abortion. This laboratory will include one additional technician and an animal handler.

LARGE SCALE TESTING

Serological studies involving 30,000 specimens from pregnant women in the Collaborative Perinatal Research Branch will be continued. Cord sera IgM and IgA levels will be determined. Supplemental sampling of the study population will be necessary to include patients who register early in the first trimester of pregnancy so that documentation of virus experience in this period will be possible.

ANTISERA PRODUCTION

Prototype sera will be prepared for 20 viruses for control testing.

ANTIGEN PRODUCTION

Additional funds for reagents will be sought so that antigens for rubella, cytomegalovirus, varicella, and new viruses will be prepared and incorporated in the testing program. Several new bacterial and protozal antigens will be added to the routine testing of the study sera.

"Myxoviruses and Multiple Sclerosis," Workshop on Contributions to the Pathogenesis and Etiology of Demyelinating Diseases, Locarno, Switzerland, June, 1967, Dr. John L. Sever.

"Serological Studies of Measles and Subacute Sclerosing Panencephalitis," Conference on Measles Virus and Subacute Sclerosing Panencephalitis, Bethesda, Maryland, September, 1967, Dr. John L. Sever.

"An Epidemiologic Approach to Subacute Sclerosing Panencephalitis," Conference on Measles Virus and Subacute Sclerosing Panencephalitis, Bethesda, Maryland, September, 1967, Dr. Stephen A. Schacher.

"Infection in the Fetus and Young Child," Symposium of The Child of a Problem Family, American Medical Women's Association, Atlanta, Georgia, December, 1967, Dr. John L. Sever.

"Progress in Rubella Vaccine Development," American Public Health Association, Miami, Florida, October, 1967, Dr. Gary L. Gitnick.

"The Process of Maternal Rubella and its Effect on the Fetus," Conference of Executives of American Schools for the Deaf, Washington, D.C., April, 1968, Dr. John L. Sever.

"Viruses and Embryos," Second International Workshop in Teratology, Japan, March, 1968, Dr. John L. Sever.

"Latex Reagent for Determing IgM levels in Cord and Newborn Sera," Federation of American Societies for Experimental Biology, Atlantic City, New Jersey, April, 1968, Dr. John L. Sever.

"Rubella Neutralizing Antibody determinations with the Rabbit Kidney Cell Strain LLC-RK$_1$ System, American Society for Microbiology, Detroit, Michigan, Dr. David A. Fuccillo, May, 1968.

"Problems in the Detection of Rubella Virus in African Green Monkey Kidney Tissue Culture," American Society for Microbiology, Detroit, Michigan, May, 1968, Dr. Carrie Whitmire (Micro. staff).

"Problems in the Study of Rubella as a Teratogen in Experimental Animals," The Teratology Society, Buck Hill Falls, Pennsylvania, May, 1968, Dr. Akinyele Fabiyi.

"Intrauterine Infection," Course on Significant Clinical Problems of Early Infancy, Children's Hospital of D.C., May 23, 1968, Dr. John L. Sever.

"Rubella Research," Seventh Annual Conference on Model Reporting Area for Blindness Statistics, Bethesda, Maryland (NIH), May 24, 1968, Dr. John L. Sever.

E. SECTION ON PATHOLOGY

Report for the Period July 1, 1967 through June 30, 1968

I. SUMMARY OF SCIENTIFIC OR PROFESSIONAL ACCOMPLISHMENTS

A. Project Material and Related Data Processing

1. Laboratory Processing

The complete gross dissection of neuropathological specimens has been done. Specimens originally reserved by some institutions for local processing have been resubmitted to this laboratory in approximately 30 instances for processing here. This in many cases is due to inadequate or altered facilities within the submitting institutions. The work-up of such partially dissected specimens is difficult because of the necessity for reconstruction of these partial dissections before our standard procedures may be applied. Work has begun on detailed microscopic study of the material resulting from submitted neurostructures. It is expected that the pace on this aspect of laboratory processing will increase with the addition of another neuropathologist to the staff in July 1968.

Heavy demands have been made upon the section for the processing of placental and autopsy material submitted in block or wet tissue form by collaborating institutions which have for one reason or another found it impractical or impossible to submit slides in finished form.

Editing of incoming Path-1, 2 and 3 forms continues and a continuous attempt is being made to reduce the backlog.

A condensed data structure, i.e., a simplified summary of pathologic diagnosis on autopsy deaths, has been a major activity of the section during this past year. The condensed data was prompted by numerous requests from various sources which required less detailed information than that provided by SNOP. The condensed data is available on tape for cohorts 1a and 1b. This summarization is a continuing process which will eventually encompass all autopsied study deaths.

2. Updating

Autopsy protocols were re-reviewed in connection with the development of the condensed data file. Updating is closely related to the development of these files and serves as a check on previous coding.

Another major activity was the parparation of final inventories of outstanding material due but not yet received in the Section on Pathology. This inventory had urgent priority within the Section during the past year. This is due to the phasing out of the pathology portion of many of the collaborating institutions. It is necessary that appropriate requests for all outstanding material be placed with the responsible institutions as soon as possible. This will permit the completion of our material (as opposed to informational) files while such material is still available from the collaborating institutions.

3. Quality Control

Two pathologists in the section were among four pathologists who reviewed lung slides on 120 cases. This study was designed in a double-blind manner and the review on the same set was repeated by the same examiner after an interval of two weeks. The objective was to determine consistency of reporting selected microscopic findings among pathologists and at the same time the consistency of the pathologist with himself. As might have been anticipated, the consistency was adequate with respect to clear-cut entities, but was reduced in those that are difficult to standardize. This activity formed an aspect of the Section's cooperation with the review efforts of the Lilienfeld Committee.

4. Full Autopsies on Abortuses

To date, approximately 70 collaborative study abortuses have been received at PRB from various collaborative institutions. These with the exceptions of a few tiny embryos have been subjected to full autopsy and a detailed narrative morphologic description made available. The small embryos which are totally unsuitable for gross dissection are being prepared in the manner of whole body serial sections. The abortus material is presumably a biased sample since there is a relatively great proportion of macerated and smaller abortuses. The results of these studies are being entered as appropriate within the data files.

B. Special Studies

1. Automated Biologic Image Processing - Collaborative Project with National Bureau of Standards

The fiscal year saw the completion of Phase I of this project. A viable programming system locally termed "LISP-PAX," was built using the Q-32 computer at Systems Development Corporation which allows the full list processing capabilities of LISP with the parallel processor simulator programs of PAX.

The system provides for the on-line input of morphologic information (i.e., "qualitative" descriptions of cell structure) with relative ease. This information may be automatically structured by LISP-PAX to essentially direct the processing of a previously digitized image.

Construction of list structures which present such "qualitative" information to the machine have begun. A "vertical" cross section of neuroanatomic information ranging from gross to electron microscopic levels has been entered, and the feasibility of machine employment of such information has been demonstrated.

The plans for Phase II of this project were completed during the year. This includes the design of connections for a borrowed galvanometer scanner to the existing LINC-8 microspectrophotometer system. This when completed will permit experiments with programmable scanning systems under control of LISP-PAX. The results of such experiments will lead to hardware specifications for the general purpose device. Initially the large computer system required for this complex will be the Q-32 which will be connected via data phone to the LINC-8. Subsequently it is hoped that connection to the DCRT based PDP-10 system will be accomplished.

During the year, the Head of the Section has participated in the design and procurement of a large general purpose computer display system, the PDP-10. A significant portion of this facility will be devoted to image processing. The contract for this system has been signed. Delivery should be complete before January 1, 1968. DCRT personnel have begun the process of implementing the transfer of LISP-PAX to the PDP-10, a task which it is hoped will be shared by NBS personnel after July 1, 1968. (Serial No. NDB (CF)-65 PR/P 1278)

2. The Length of the Umbilical Cord

Due to excessive demands on data processing facilities by other commitments and personnel shortages, there has been no significant progress on this project. (Serial No. NDB (CF)-66 PR/P 1342)

3. Influencing Factors in Sudden Unexpected Death

The pathology portion of the study on sudden unexpected death is completed. The evaluation of clinical data by the Section on Pediatric Neurology is still in progress. (Serial No. NDB (CF)-66 PR/P 1345)

4. Placental Changes After Experimental Abruptio and Fetal Vessel Ligation of Rhesus Monkey

After vascular ligation of fetal vessels using Rhesus monkey placenta at 100-120 days gestational age, syncytial trophoblasts and cytotrophoblasts were found to be still growing 40-50 days after treatment. The villi in the treated lesions were few, large and fibrotic. There were neither intervillous fibrin deposits nor thrombi in the wide intervillous spaces. Because of the sparsity of villi, the syncytial trophoblasts were seemingly increased in amount. The monkey fetuses appeared to tolerate the insult of fetal vascular ligation, but experimental abruptio placentae resulting in derangements of the maternal circulation caused fetal death in utero. This has been published in the American Journal of Obstetrics and Gynecology. (Serial No. NDB (CF)-66 PR/P 1351)

5. The Neuropathological Study of a Series of Selected Monkey Brains from Animals in the Perinatal Period

This study of 103 selected perinatal monkey brains is designed to provide a morphological information base for experimental designs dealing with perinatal injury in primates. The protocol development and morphological observation is proceeding at a slow pace due to professional personnel shortages. (Serial No. NDB (CF)-66 PR/P 1352)

6. A Sequential Study of Ultrastructural Changes in an Experimentally Produced Traumatic Brain Lesion

The objective of this study is to provide timed data as to glial cell response to direct traumatic injury, employing initially mice. This will eventually provide a base for anticipated studies in primates.

The period has largely been devoted to technical aspects, i.e., the processing of large epoxy sections for combined light electron microscopy, which were successfully applied during the reporting period. This will permit the last stage of the project to be attacked. (Serial No. NDB (CF)-66 PR/P 1353)

7. Automated Microspectrophotometry Employing the LINC Computer

During the year, the borrowed LINC computer was replaced by a purchased LINC-8 which permitted the resumption of this project. The interfacing of the computer to the microspectrophotometer subsystem was completed during the fiscal year. Preliminary designs for a further interface of a scanner developed by Perkin-Elmer for NCI (now on loan to us) were begun during the reporting period. (Serial No. NDB (CF)-66 PR/P 1354)

8. Factors Influencing Quantitative DNA Staining

Further progress in this project concerned with the kinetics of staining and stain fading has been delayed due to the need to switch over from the LINC to the LINC-8 microspectrophotometer system. With the completion of the interface of the microspectrophotometer, work on this substantive project may resume in parallel to the scanner interfacing. (Serial No. NDB (CF)-66 PR/P 1355)

9. Diagnosis of Sickling by Placental Examination

When the placenta separates from the uterine wall the resulting hypoxia creates a natural sickling preparation of the trapped erythrocytes in the placenta. A histologic examination of 2,117 consecutive placentas of Negro women enrolled in the collaborative study showed a sickling incidence of 9.4%. Sickling rates in the southern institutions (11.0% - 12.2%) were higher than in the northern institutions (6.1% - 8.4%). It is postulated that these geographic differences in sickling rates may indicate increased admixture of Caucasian blood among northern Negroes. Permanent histologic sections of the placenta offer the advantages of retrospective study, uniformity of technique and reconfirmation of diagnosis, which are not possible with sickle-cell preparations on peripheral blood. The first phase of the study has been published in the American Journal of Obstetrics and Gynecology. The study will be continued, comparing maternal sickler's and non-sickler's regarding selected factors. (Serial No. NDB (CF)-67 PR/P 1517)

10. Preparations of Large Epoxy Sections for Light and Subsequent Electron Microscopy

This project, which has resulted in the successful development of methodology for sequential light and electron microscopy, may now be regarded as complete in that it has been successfully applied to problems within the laboratory (e.g., Individual Project NDB (CF)-66 PR/P 1353) and has been published and exhibited on several occasions. (Serial No. NDB (CF)-67 PR/P 1518)

11. The Study of Unilateral Thickening of Fetal Arteries on the Placenta

Unilateral thickening was observed in the lower wall of fetal arteries on the placental surface adjacent to the intervillous space. The unilateral muscular growth seemed to have its onset at 12 weeks gestation increasing in frequency with increments of gestational age and later being associated with intimal thickening in the term placenta. Out of 202 consecutive term placentas, 84.1% or 170 placentas showed this

peculiar thickening of the lower arterial wall by the single cross section. In contrast to atherosclerosis, the medial muscular growth was more pronounced than the intimal thickening and there was no remarkable lipid deposition. The etiology of such unilateral lesion is discussed in relation to the pathogenesis of atherosclerosis. This has been published in the American Journal of Obstetrics and Gynecology. (Serial No. NDB (CF)-67 PR/P 1519)

12. Congenital Malformations in Perinatal, Infant and Child Deaths

Congenital malformations in perinatal, infant and child deaths were analyzed according to strict criteria. Rates for each type of death and sex were consistently higher in whites than in Negroes. Single malformation rates in neonatal deaths were twice as high in males as in females. Multiple malformations were commong in white females, especially stillbirths. The general incidence was not significantly higher in the extremes of maternal age except in white females where the high rate in those 19 years old or less was mainly due to multiple defects. Malformations appeared to play a relatively small role in the premature compared to the mature baby that died. The lack of clustering of associated malformations at the specific critical time period when the selected malformation was expected to have occurred demonstrates the etiologic complexity of this problem in humans. This paper is being prepared for publication in the American Journal of Obstetrics and Gynecology. (Serial No. NDB (CF)-68 PR/P 1649)

13. Placentation in Relation to Zygosity of Twins

A comprehensive review of 600 twin placentas in the collaborative study is being undertaken and the relationship is being studied of each specific type of twin placentation to zygosity, birthweight differentials, sex and gestational age. (Serial No. NDB (CF)-68 PR/P 1650)

14. The Ultrastructural Evaluation of Developing Hyaline Membranes in Strain A Mice

An experimental study is in progress to determine the pathogenesis of pulmonary hyaline membranes in mice following various lengths of exposure to high oxygen. Light and electron microscopic techniques are being utilized. (Serial No. NDB (CF)-68 PR/P 1651)

15. Ultrastructural and Histochemical Evaluation of the CNS in Mice Progeny when a Protein-Deficient Diet was Administered During the Second Half of Gestation

The role of the Section in this exploratory project is to provide morphological support to this interdisciplinary study. The morphologic results are now in the process of being abstracted from the prepared sections. (Serial No. NDB (CF)-68 PR/P 1652)

16. Correlative Light and Electron Microscopic Pediatric Pathology

The fundamental problem of light microscopic and electron microscopic correlation is dependent on the possibility of sequential examination of the same structures. In order to provide suitable standards for organs other than brain, Dr. Carleton has been detailed for a six-month period to Ohio State University in order to collect and preprocess suitable tissues from a general pathology department. This first phase is still in progress at this writing. (Serial No. NDB (CF)-68 PR/P 1653)

C. Other Activities

Dr. Lipkin has served as contract officer for the collaborative program with the Artificial Intelligence Group of the National Bureau of Standards as described in the Individual Project Report.

The Section Head continued his working relationship with the Image Processing Group, DCRT. During the reporting period, specifications formed during the previous year resulted in a contract between DCRT and the Digital Equipment Corporation for the purchase of a PDP-10 computer display system.

II. PROBLEMS

Within the neuropathologic unit, the effort on microscopic review is seriously hampered by the shortage of neuropathologists. Considerable acceleration of this activity is expected due to the successful recruiting of a neuropathologist, Dr. Oscar Aparicio, who will begin his duties July 1, 1968.

Additional neuropathologic man hours should be made available during 1968-1969 due to the recruitment of a full-time electrical engineer to manage the LINC-8 microspectrophotometer, thus allowing the Head of the Section to devote more of his time to neuropathologic review.

The problems (separation of personnel and files) occasioned by the physical separation of the two parts of the Section should be corrected by the move to the new building during 1968-1969. This will make total case review a feasible reality.

The loss of the space in the new designated quarters for histochemistry constitutes a serious blow to the projected programs in experimental pathology, before they are even begun. Some replacement of this loss must be made if the laboratory is to be concerned with anything beyond purely morphological studies.

Lack of clerical or subprofessional personnel has been a chronic and major problem in the Section. New problems have arisen as a consequence of the rapid phasing-out of pathology units in the various collaborating institutions. On the one hand, there are deluges of slides arriving from certain institutions creating a problem of logging-in and filing. On the other hand, there seems to be considerable inertia in other institutions to submit outstanding required material, necessitating the use of other than the usual methods for obtaining the desired material. This requires extensive inventories for which additional clerical help is necessary. On occasion, this Section has had to supply assistance and information over and above what should be expected.

Another problem created by the phasing out of pathology is that concerning current deaths. Deaths, albeit few, continue to occur but as pointed out by one institution, there are no longer any project personnel to perform the work with the result that the post-mortems have had to be done cursorily by non-project personnel. Unfortunately, these involve such conditions as chronic neurologic disorders, congenital malformations, tumors, etc. A provision must be made that these post-mortems be done with the same excellence as before, but now on a fee-for-service basis.

III. PROPOSED FUTURE OBJECTIVES

The move to new quarters and the addition of two new professionals should now make possible the reorganization and integration of the Section into a functional unit whose routine activities will be data development from the now processed neuro and general pathologic material.

The Section will be in a position to begin the reaping of the return on the long and large investment in the image processing and micro-spectrophotometer projects, as well as that in the DCRT image processing facility. The various aspects of these heretofore separate projects are now approaching each other so that it may be possible to unify them in fact, as they have been from the beginning in concept.

Established research projects will be pursued as detailed in individual reports.

F. SECTION ON EPIDEMIOLOGY AND GENETICS

Report for the period July 1, 1967 - June 30, 1968

I. SUMMARY OF SCIENTIFIC AND PROFESSIONAL ACCOMPLISHMENTS

During the past fiscal year the research activities of this Section were slowed down considerably because of the heavy administrative demands made upon it by the operations of the Lillienfeld Committee. A major effort was made to continue and expand the research activities and complete as many of the ongoing research projects as possible. Thus, a number of projects have been completed and prepared for publication and many new projects within the scope of the program have been initiated; others are still in progress. Some examples are given below and detailed descriptions of all projects are given in the individual project reports. Constant efforts have also been made to update and complete our data file and to obtain copies of missing records from the participating institutions.

The Section has continued to receive, edit and code information on the FHH-9 form. During this period approximately 5,500 FHH-9 forms were received. Of these 4,500 were edited and coded and 3,500 were sent to punch. A total of 95 SE-1 forms and 1,325 GEN 5-8 forms were also received and processed but these include copies of missing forms requested from the various institutions.

The determination of zygosity of twins born to study mothers continues. To date 620 pairs of twins have been identified. In spite of repeated pleas to the Project Directors to submit the required finger and palm prints, these materials are still missing for 72 pairs of twins.

A number of studies has been completed and the results have been published. The study of the socioeconomic index was further refined with controls for age, race, region and size of urban area, for comparisons of our population with the U. S. population, and is being published in Social Science and Medicine, a new international journal. The genetic study of Parkinsonism produced by ataraxic drugs has also been completed. The results were reported at the Parkinson's disease symposium of the 2nd International Congress of Genetics and Neuroophthalmology. The first phase of the Comparative Study of reporting of various congenital malformations has also been completed. It showed that only 46.4 percent of clefts present in Study babies were reported on their birth certificates. The methodological study of the properties of Woolf's statistic for analysis of 2x2 tables has been completed and was reported in Biometrics.

A number of studies are still continuing. Children with cleft gum (see above) are being examined to determine if a bony defect underlies the soft-tissue cleft in this newly recognized abnormality. The study of birthweight has been extended to compare children in the 100th percentile of weight with those in the 50th percentile of weight, in terms

of several socioeconomic and medical variables. The study of major congenital malformations has also been extended to utilize the complete cohort in order to investigate those relationships which were shown to be significant in the preliminary study. The study on population dynamics of Tay-Sachs' disease has been extended to include several other lipidoses and to determine whether resistance to tuberculosis or some other infectious disease confers a selective advantage to the heterozygote. Several other projects are at varying stages of completion.

Among new projects initiated last year are: a detailed evaluation and comparative study of the Puerto Rican cohort in the Collaborative Study; a study of physical growth of children in the Collaborative Study; further investigations of the socioeconomic index as a descriptive and predictive instrument; and, development and evaluation of an index of reproductive performance for the purpose of identifying high risk pregnancy suspects.

Drs. Naylor and Bartlett contributed significantly to the development of our program during the past year. Dr. Naylor, the population geneticist of the Section, has been involved in various projects for a number of years. He has been instrumental in designing the analysis of many of the studies mentioned earlier, often doing the programming himself. He has also assisted in the rheumatoid arthritis program of NIAMD as an epidemiologic consultant. Dr. Bartlett, our medical sociologist, in addition to his own research, has provided considerable analytical assistance to the office of the Assistant to the Chief, expecially in the Georgetown University Retrospective Mental Retardation Study and the Public Health Implications Study.

With the shift from grant to contract operations for the collaborating institutions, this Section has become actively involved in the administration of the project. Dr. Myrianthopoulos is the project officer for two institutions, Columbia University and New York Medical College. As such he has participated in contract negotiations, made recommendations concerning the budget, authorized payments and made frequent visits to these institutions to discuss problems and insure the fulfillment of the contract.

The Section has participated in the quality control program in a test-retest of the FHH-9 between Boston and Richmond. It has also held two workshops for the FHH-9 for the interviewers at Johns Hopkins Hospital and the Medical College of Virginia.

The Section has been concerned considerably with ways and means to help maintain the sample. Mrs. Vincent spent much of her time visiting participating institutions, reviewing with them their sample maintenance problems, and actually helping to locate families with unknown addresses which were given up as lost to the Study.

II. PROBLEMS

The two main problems which this Section continues to face are the shortage of trained professionals to analyze the mass of the collected data and the slowness of computer operations in furnishing the materials and providing programs for these analyses. The shortage of trained professionals was relieved somewhat by the decision to invite qualified research workers from outside the project to participate in the analysis of the genetic and socioeconomic material. Among scientists who are actively participating in the analysis of our data are: Dr. Stanley Aronson from the State University of New York; Dr. C. S. Chung from the University of Hawaii; Dr. Bernice Cohen and Mr. Joseph Sayre from Johns Hopkins University; Dr. Herman Slatis from Michigan State University; Dr. Dorothy Warburton from the College of Physicians and Surgeons of Columbia University; Dr. Joshua Lederberg from Stanford University; and Mr. Craig Humphrey from Brown University.

Dr. Bartlett will be leaving this Section at the end of June, 1968, to complete his pediatric training. He plans, however, to maintain close contact with us and work on projects which he started during his stay here. We are actively recruiting for a replacement for his position. We are greatly pleased to welcome to this Section Dr. Valerie Cowie, who will spend a year with us, beginning October, 1968, as a visiting scientist. Dr. Cowie is a British scientist widely known for her work in the genetics of mental retardation.

The slowness of computer operations, during the past year had become more and more serious, resulting in delays of from 3 to 6 months for an approved request to be processed even if the end product was nothing more than simple tabulations. These delays caused considerable frustration to us and embarrassment to our collaborators. There are already signs of improvement in data processing and retrieval.

III. FUTURE OBJECTIVES

The research program of this Section is progressing according to our long-range plans, outlined in earlier reports. The objectives for the future are: to strenghthen our professional staff; to expand the scope of our investigations so as to utilize all the important genetic and socioeconomic variables in investigations of specific problems which are defined from the first round of analysis; and to create laboratory facilities for biochemical, genetic and cytogenetic investigations. The last two objectives are now taking definite shape. Space has been provisionally alloted to us in the new NINDB-NIMH building to establish the biochemical and cytogenetic laboratories. We are now actively recruiting for professionals and technicians to staff them. It is anticipated that the laboratories will begin operation in October, 1968.

IV. MISCELLANEOUS

A. Personnel

The personnel of the Section on Epidemiology and Genetics consists at present of the following: Professional, Dr. Myrianthopoulos, Head, Dr. Naylor, Geneticist, Dr. Bartlett, Medical Sociologist, Miss Martin, Statistician; other, one secretary, one clerk typist, five coding clerks.

Mrs. Vincent, the Senior Nurse Officer, retired in March, 1968. We are actively recruiting for a replacement for her position. Dr. Valerie Cowie will join this Section, as a visiting scientist, in October, 1968. We are also actively recruiting for a biochemist and a cytogeneticist to staff the laboratory part of our program.

B. Activities of the Section Head and the Professional Personnel

The head of the Section, Dr. Myrianthopoulos, in addition to his formal duties has carried out independent investigations in the genetics of neurological disorders. Dr. Myrianthopoulos has maintained his affiliation with George Washington University as an associate professor of Neurology and Director of the Genetic Counseling and Research Center. In this capacity he gives a series of lectures in the medical school and conducts genetic counseling upon referral by individual physicians. Dr. Myrianthopoulos is also a member of the faculty of the graduate program at NIH where he gives a course in human genetics.

In September, 1967, Dr. Myrianthopoulos attended the Second International Congress of Neurogenetics and Neuroophthalmology which he helped organize, in Montreal, Canada. Dr. Myrianthopoulos delivered the keynote address at the symposium on Huntington's chorea and read a paper on his work in drug-induced parkinsonism.

Dr. Myrianthopoulos was invited to serve on the Committee on Huntington's chorea of the World Federation of Neurology, whose function is to promote interest and research in Huntington's chorea. The Committee held its first meeting in Montreal during the Congress. In March 1968 the Committee held a three-day "think session" at the Mayo Clinic, in Rochester, Minnesota.

Dr. Myrianthopoulos was elected to the scientific branch of the Huntington's Chorea Foundation, a private organization formed to support research in Huntington's chorea.

Dr. Myrianthopoulos participated in a genetics seminar at Howard University, Washington, D. C. and in the special courses of the American Academy of Neurology, Chicago, in April 1968. Dr. Myrianthopoulos also participated in many meetings and conferences and presented lectures in various scientific groups throughout the

year.

Dr. Bartlett visited a number of medical centers in Great Britain that are carrying on work related to his interests in medical sociology. Among these were: The Medical Sociology Research Unit, University of Aberdeen, Scotland; the Department of Child Life and Health, University of Edinburgh, Scotland; St. Mary's Hospital Home Care Unit, London, England; Paediatric Research Unit, Guy's Hospital Medical School, London; the National Birthday Trust Fund and National Child Development Study, London; and the Department of Paediatrics, University of Bristol, England. These visits provided Dr. Bartlett first-hand knowledge of work going on elsewhere and the opportunity to make personal contacts in his area of interest, as well as to acquaint other workers with details of the Collaborative Study.

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G. SECTION ON DATA MANAGEMENT AND RETRIEVAL
Report for Period July 1, 1967 through June 30, 1968

I. SUMMARY OF ACCOMPLISHMENTS

This Section, established during the past year, is entrusted with the task of receiving, coding, filing and storing forms in accordance with a system designed to facilitate form and/or data retrieval, as well as computer programming. The Acting Head of this Section is on detail from the Office of Biometry.

The total number of women registered in the 12 study institutions as of December 31, 1965 (the closing date for all such registrations) as adjusted was 58,845 -- of this number 56,203 were core study cases. Of the number of core study cases 53,749 have delivered with the last delivery on September 30, 1966.

Over 3.1 million forms will have been submitted by June 30, 1968. The available data from approximately 2.7 million forms has been processed into over 4.9 million punch cards in 111 card formats and converted into active computer tape files. The backlog in editing and coding consists of slightly over 134,000 forms. 46,736 births have been studied at 1 year of age, 24,958 at 4 years of age and 5,660 at 7 years of age.

During the year the Perinatal Research Branch has continued development and use of complete program packages to provide PRB controlled card update and editing to PRB operated master files and data banks, thus eliminating dependence in this area on contract programming.

In addition to supporting the research activities of PRB with special information retrieval for case selection and informational tabulations, the Section has produced 155 sets of tabulations and large-scale studies involving large amounts of data, extensive systems analysis and complex data processing.

The review of unaccounted-for study forms started at the end of F.Y. 1966 was completed in F.Y. 1967 and repetition of the review to add 1965 was accomplished in F.Y. 1968 involving recontacting the institutions for records missed or not retrieved as a result of the prior review. Also, extensive sets of tabulations and reports were prepared for use of the special review committee (Lilienfeld Committee).

II. PROBLEMS

Our problems are in two areas:

1) As the program has matured, the Section, which contains large numbers of non-professional staff, has required major shifts in the assignment of personnel including retraining where required. This has led to chronic shortages of personnel for temporary periods and requirements for use of

part-time personnel to meet needs of the Branch.

2) A basic problem has been the necessity of contracting for data processing services on an annual basis in lieu of every three to five year basis. Change of contractors can result in initial loss of effectiveness due to the learning process involved in the job order data processing requirements of the extremely large data bank of PRB.

III. PROPOSED FUTURE OBJECTIVES

The Section expects to continue to develop its programming strength and to make itself more independent from outside programming needs. Now that the input and file procedures are set up and the data base is a relative constant, sophisticated information retrieval compliers can be developed to supply research needs more rapidly and accurately. The conversion and retraining of staff will continue so that, except for reductions by attrition, present personnel can be reassigned to new current functions of the Section. New systems development are underway which will effect reduced turnaround time on study requests as well as economy of operation.

H. SECTION ON PROJECT SERVICES
Report for Period July 1, 1967 through June 30, 1968

I. SUMMARY OF ACCOMPLISHMENTS

The past year has been exceptionally busy for Medical Literature Service. The Perinatal Research Branch with its increase in professional staff resulted in an increase in requests for service, thereby adding to our workload. The newly created Office of Biometry has also availed itself of our services.

Reading Room

The PRB Reading Room now has a collection of books totalling 697. The collection includes medical, statistical textbooks, scientific directories, annual publications of books and periodicals in print, etc. Approximately 82 books have been added to our shelves since the last report. Our journal subscriptions number 106 including 16 abstracting periodicals, an increase of 11 since the last report. The locater file, which is a control of medical, technical and statistical books in PRB offices, other than those in the Reading Room, now totals 941, an increase of 28 new acquisitions during this fiscal year.

Approximately 1251 persons visited the library and used its facilities. A total of 1020 textbooks and journals were borrowed by PRB Staff from the Reading Room.

Reprint File

Our reprint collection and retrieval file now totals over 7000. These are retrievable by author, subject and numerically. Thus far approximately 4800 have been indexed according to subject. In addition there are approximately 600 reprints in different stages of processing and which will eventually be added to the collection. The collection is comprised of reprints acquired as a result of searches in the literature for articles of critical interest to the Staff and pertinent to the Study. This file is steadily enlarging. Subject headings are patterned after those listed in Index Medicus and include a great majority of them. This phase of our work is progressing rather slowly due to reduction in staff during the last fiscal period.

Bibliography

Work continues on bibliography of Project publications which embraces pooled and local core data as well as publications by PRB personnel not related to the Project. This is updated periodically. Copies are available for distribution.

Separate bibliographies of Project publications based either on core data or local core data are also maintained.

A bibliography of Collaborative Project publications, by institution, was prepared for the Lilienfeld Committee and included the following categories: (a) pooled core data, (b) local core data, (c) publications using collaborative Project population, (d) publications of personnel supported in part or in toto by Collaborative Project funds, and (e) ancillary studies. We are now in the process of collecting reprints for these references. Again work is progressing slowly o.. this score due to reduction in staff.

In addition, the following bibliographies are on file covering the subjects listed below. A few are MEDLARS searches requested by PRB Staff. These are in addition to the ones reported last year:

Amino Acid Transport in Non-human Mammals
Clinical Research on Drugs with Epilepsy or Convulsions-1966 only
Factors Associated with Deafness in Very Young Children
Electronystography
Galactosemia
Hereditary Aspects of Retinitis Pigmentosa
Human Fetal Cardiac Function
Human Laterality in Learning and Aphasia
Human Reproduction - Carl G. Hartman
The "Imprinting" Phenomenon
Innervation of the Iris
Intelligence in Twins
Intelligence Level in Offspring of Diabetic Mothers.
Intrauterine Fetal Weight
Ketoacids in Diabetes, Especially in Pregnancy
Publications of Warren H. Lewis from 1947 - 1958
Listeria Monocytogenes
Mongolism
Stuttering related to Organic Brain Damage
Subacute Sclerosing Leucoencephalitis
Surgical Aspects of Temporal Lobe Epilepsy, Including Statistical Analysis of Selected Factors

Demand or Loan Service

During the past year, Medical Literature Service Unit procured from NIH-NLM Library, 296 books and journals for use of PRB Staff. In addition, 8461 photocopy requests of reprints were procured as requested by the various sections with the breakdown as follows:

Office of the Chief	826
Section on Behavioral Sciences	124
Section on Epidemiology & Genetics	417
Section on Infectious Diseases	736
Section on Obstetrics	906
Section on Pathology	286
Section on Pediatric-Neurology	1348
Section on Speech, Language & Hearing	88
Section on Data Management & Retrieval	8

Section on Statistical Analysis	7
Medical Literature	3523
Miscellaneous	192
Total	8461

Reprints of articles requested by PRB Staff and reproduced in our xerox room totalled 5998. This total is included in the individual breakdown by Sections.

In addition to routine requests, the Section provides "Demand Service". This is "on the spot" acquisition of literature, urgently needed by the professionals from NIH Library, and which is not available in PRB Reading Room. Trips are made upon request thereby saving considerable professional time. Usually the material requested is acquired on the same day.

Miscellaneous Activities

The Unit conducts literature searches upon request covering specific searches for references by author and subject. Also searches books and periodicals to retrieve articles or chapters under general topic requested.

Incoming journals and book reviews are perused for new publications pertinent to the Study or of critical interest to a discipline and brought to the attention of the professionals.

Independent searches in the literature and independent contact with a variety of authors and libraries are conducted to acquire additional information of potential usefulness to the various professionals connected with the Project.

Verification of references in compilation of bibliographies for Collaborative Project studies before being submitted to journals for publication is done upon request.

Prepares and distributes periodically, to PRB Staff, Collaborators and outsiders using our facilities, updated bibliography of Collaborative Project Publications, lists of new books, journals and abstracts, etc., keeping them up to date on new acquisitions.

The unit answers a variety of requests from science writers and others who write to PRB inquiring about Collaborative Project publications. This activity involves public relations and dissemination of information upon request.

II. PROBLEMS

We are faced with a considerable backlog due to reduction in force during this fiscal period. The Unit now consists of 1 supervisory clerk, 1 library assistant and 2 clerk-typists (one half-time).

In August 1967, we were forced to move to smaller quarters. The lact of potential growing space for the ever-increasing journal literature and updated scientific books poses a problem which needs to be considered.

III. PROPOSED FUTURE OBJECTIVES

To eliminate backlog; to continue to serve PRB Staff meeting their individual needs for reference searches, compiling special bibliographies, etc., as requested. To familiarize ourselves with subject matter of proposals being processed and endeavor, to the best of our ability, to search incoming literature and being on the alert for articles dealing with subjects under study, and passing this information on to professionals involved. In service training in Library Science or related fields is available to MLS personnel when indicated.

I. SECTION ON SPEECH, LANGUAGE AND HEARING
Report for the Period July 1, 1967 through June 30, 1968

I. SUMMARY OF SCIENTIFIC AND PROFESSIONAL ACCOMPLISHMENTS

The 3-Year Speech, Language and Hearing Examination. Data in-flow has proceeded smoothly and continues to receive close editorial supervision for detection and correction of errata. Records are no longer being received from Boston and Philadelphia, which were using home-screening methods for case detection, nor from Columbia which has finished testing all 3-year olds. Site visits have been made to all participating institutions, except Buffalo, mainly in the course of quality control trials at these institutions. Sound level measurements and audiometer calibration checks were performed at most test facilities in a continuing effort to monitor conditions at examination. Three rounds of quality control exchanges have been completed and the fourth has been initiated recently. The results of quality control retests and a tabulation of examination results by institutions and subtests were provided to every speech, language and hearing examiner and discussed during the first day of a three-day workshop held at Memphis in September, 1968. These efforts have been undertaken to reduce the appreciable variations in examination findings between institutions.

The Final Speech, Language and Hearing Examination. Following a limited pretest at several institutions, the examination and results available at the time were discussed during two days of the 3-day workshop for all speech, language and hearing chiefs and examiners. The examination was demonstrated in the course of discussions. A number of changes were made in administration and scoring. The examination is being used in essentially the pretest form. Results are in process of tabulation for the purpose of setting cut-off points for scoring. A summary sheet is being devised. Philadelphia has become a participant in this part of the study and is currently administering the exam to all 8-year olds enrolled at that institution. Examinations Providence have been moved from Rhode Island Hospital, which had a poor record of inadequate exams and numerous retests at the 3-year level, to a new test facility in the Child Development Study where examinations can be done under closer supervision.

Summary of Data Collection and Processing as of March 31, 1968

	3-Year Exam.	Final SLH Exam.
Total forms received in Section:	21,028*+	985
Total forms sent to punch:	17,367	--
Backlog awaiting processing in Section:	3,661*	985
Forms received 7-1-67 to 3-31-68:	3,294*	985
Number projected to 6-30-68:	4,392	1,486

*Includes repeat examinations and duplicates
+This figure does not include Screening Examinations from Boston (total number received through March 31,1968=6,121) and from Philadelphia (total number received through March 31, 1968 = 3,423).

II. PROBLEMS

A. Personnel

The staff of the Section on Speech, Language and Hearing consists, as before, of two statistical clerks and one professional level audiologist. The audiologist is the Section Head and, until December, 1967, functioned also as Acting Head of the Section on Behavioral Sciences which activity commanded a considerable portion of his time and attention. Because of frequent travels in connection with subcommittee meetings, quality control visits and duties as project officer to two institutions, the clerks have been put under the immediate supervision of the Statistical Assistant in the Section on Behavioral Sciences. There is continuing need for at least one other audiologist or speech pathologist to share in the demands of the Section. Efforts to recruit at the doctoral level have not been successful due largely to the poor competitive position of government salaries compared with the universities and other non-governmental positions in this area of activity. There is reasonable likelihood, however, of obtaining a speech pathologist at the masters degree level in August, 1968.

The Section still does not have a secretary. This function is being served by the secretary in the Section on Behavioral Sciences. The demands upon that secretary are being increased to the extent that additional help is required.

B. Space

Relocation has resulted in closer integration of activities with Behavioral Sciences as recommended in the previous report. Space allocation is currently adequate due, in part, to the small size of the Section on Speech, Language and Hearing.

III. PROPOSED FUTURE OBJECTIVES

A. Results from the 3-year Speech, Language and Hearing Examination will be analyzed to relate communicative status to selected variables in the developmental history of the Study population. The effectiveness of this examination will be evaluated in terms of identifying deficiencies in the performance of Study children as compared with other measures used in psychology.

B. Data from the 3-year exam will be compared with those from the Final Speech, Language and Hearing Examination to estimate the significance of early detection of communications problems with regard to their outcome with and without therapeutic intervention.

C. Summary scoring of the Final Speech, Language and Hearing exam is in process of being devised and will be completed in the near future. Efforts will be made subsequently, by means of statistical analysis, to derive from the battery an index of communicative efficiency similar to the Intelligence Quotient.

D. Efforts will continue to encourage ancillary studies and data analyses at the local institutional level where activity of these kinds have not been in evidence to date.

E. Pursuit of special studies relating to specific learning disabilities.

IV. MISCELLANEOUS

Present staffing of the Section on Speech, Language and Hearing is not adequate for the requirements of a serious concern with this facet of perinatal research. Unless this section can be enlarged to the level of a functional entity it is not realistic to expect effective operation on other than a caretaker basis. Effective review and use of the data requires the addition of two professional level SLH persons (one of which is expected to join the Section in July, 1968) plus two statistical assistants to support their efforts. The need for a secretary is already being felt and will become acute with these additions.

Efforts will be made by the Section, when staffed, to establish liaison with the appropriate graduate divisions in the local universities in order to utilize available data in graduate theses and thereby promote multidimensional evaluation and extension of these data. The recommended increase in staffing will serve also to enlarge the competence of the Section as a resource unit for the Institute which, although providing broad extramural support of activities in the speech, language and hearing area, houses no other group in this specialty.

Serial No. NDB (CF)-57 PR/ID 402
1. Perinatal Research Branch
2. Section on Infectious Diseases
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Serological and Virus Isolation Studies of Infectious Diseases in the Collaborative Study on Cerebral Palsy, Mental Retardation, and Other Neurological and Sensory Disorders of Infancy and Childhood.

Previous Serial Number: Same

Principal Investigators: Dr. John L. Sever, PRB, NINDB
Dr. David A. Fuccillo, PRB, NINDB
Dr. Robert J. Huebner, NIAID

Other Investigators: Dr. Akinyele Fabiyi, PRB, NINDB
Dr. Gary Gitnick, PRB, NINDB
Dr. Jane Todaro, PRB, NINDB
Dr. Gary Birnbaum, PRB, NINDB
Dr. James Overall, NICHD
Anita Ley, PRB, NINDB
Renee Traub, PRB, NINDB
Mary Ruth Gilkeson, PRB, NINDB
Collaborative Institutions in the Perinatal Research Study

Cooperating Units: Laboratory of Infectious Diseases, NIAID
NICHD
Cooperating Institutions in California and Hawaii (with the Section on Infectious Diseases)

Man Years:

Total:	14.5
Professional:	5.5
Other:	9.0

Project Description:

Objectives: The purpose of the infectious disease investigations in the Perinatal Research Study is to determine insofar as possible the role of infections in the production of abnormal pregnancy outcomes. To accomplish this serial specimens are taken throughout pregnancy, at delivery, and at six weeks post partum. These sera are being tested with antigens to determine the antibody responses of the patients during pregnancy and post partum, and then to relate this serological information to the clinical data for the pregnancy

and the child. In addition, placenta specimens for virus isolation and serum specimens from the children at one year of age were obtained from the last 10,000 study pregnancies and these are now being studied. In special cases when congenital infection was suspected on the basis of clinical or laboratory findings, throat swabs and blood specimens were obtained from the children.

Methods Employed: To accomplish this program blood specimens were obtained from pregnant women at set intervals throughout pregnancy and post partum. Initially, during 1959 the collection of blood specimens was made once every trimester. Late in 1960 the requirements for the collection were increased and strengthened so that blood specimens were taken at the time of registration, at set intervals of approximately every two months throughout pregnancy, at delivery, and at six weeks post partum. At the same time a uniform method for the collection and processing was adapted as a required study procedure. The use of special Vacutainers, sterile technique, special sterile vials, and new shipping containers were all required. Intensive laboratory training sessions were held at NIH by the Section on Infectious Diseases for all technicians in the collaborating institutions. These sessions were repeated each year and a training film was prepared and sent to collaborating groups on request. Careful, complete control was maintained on all collection and processing of serum. At the Serum Center of the Section, personnel checked every vial of serum as received for quality and quantity. Regular reports of this information were sent every three months to each study institution. Telephone calls were made immediately to Project Directors whenever there was a decrease in the quality and quantity of sera received. Completeness of sets of specimens from each patient was also reviewed by Serum Center personnel. To improve the collection of complete sets of sera a special reporting form was devised for the collaborating institutions and monitored by the Section.

By the spring of 1961 all institutions attained the minimum requirement of 90% satisfactory specimens for quality and quantity. Satisfactory quality was defined as straw colored sera with no hemolysis. Satisfactory quantity was a minimum of 4 vials, each with 3 ml of serum and proper labels. At each meeting of the Project Directors a report was given concerning the quality and quantity of specimens submitted by each institution. This detailed intensive review was conducted throughout the entire time of sampling of sera from the mothers and continues at present with specimens being received from children at one year of age, special study specimens, and sera from cooperating groups.

Completeness of sets of serial specimens was determined from the sera submitted to the Serum Center of the Section and the special reporting form sent to the Section. Data for the first 28,386 patients showed that there was at least one specimen submitted for 94.2% of the patients. The majority of the omitted specimens occurred during the first months of 1959. A computer analysis of specimen set completeness is being prepared at the present time.

With the development of a firm base for obtaining the required specimens and tissues, the program embarked on a large commitment for the development of necessary antigens, new techniques, and the training of a competint laboratory

staff for the study of the specimens. Antigen development was conducted by the personnel of the Section and experienced investigators under contract. Professional laboratory personnel were selected for the Section's Units on Statistics and Design, Serology, Virology, Experimental Animal Research, Immunological Studies, Epidemiology, and Experimental Pathology and Neurology. Three years ago, two additional units were added. These were the Units on Cytogenetics and Vaccine Development. These programs are jointly sponsored with the National Institute of Child Health and Human Development and the National Institute of Allergy and Infectious Diseases with the National Institute of Neurological Diseases and Blindness.

To document the occurrence of an infection, two approaches are available: 1) Isolation of the microorganism from the patient or 2) Detection of an antibody rise in serum specimens. Both approaches are being used in the present studies. Appropriate isolation procedures for virus, bacteria, and protozoa are being used with placenta and throat swab specimens from the children. This approach was not used for detecting infections in the mothers since it would have required obtaining throat swab and anal specimens at the time of each infection. When this has been tried in the past, it has been unsuccessful because the women are usually unable to come to a laboratory for the collection of specimens when they have minor illnesses. Furthermore, a great many of the infections under consideration frequently do not result in significant illness of the women. These subclinical infections go unnoticed and unrecognized. For these reasons, the serological approach was selected. By collecting serial serum specimens, antibody levels for various viruses and protozoa can be determined. The development of antibody to a microorganism in a patient who was previously antibody negative provides indirect evidence for infection. The presence of specific antibody indicates prior exposure to that antigen or microoganism.

The serological test most frequently employed in these studies is the complement fixation method. This basic method has been used for many years as the Wasserman test for the diagnosis of syphilis. With the use of viral antigens the test is very versatile, performed rapidly, and provides broad coverage of a great many of the more than 125 viruses which are known to be of importance to man. Antigens were prepared for most of these viruses. Tests of specificity were conducted with animal sera. For man, considerable data is available from our studies and those of many other laboratories to indicate that both group and specific reactions occur with these antigens. The adenovirus CF (Type 2) antigen, for example, is group reactive and provides evidence for adenovirus infections in general. To date, there are 31 adenoviruses recognized for man. Rubella CF antigen on the other hand is very specific and detects infection with rubella only. The sensitivity, specificity, and persistence of the test is also known. With this type of information, it is possible to design serological studies for the viruses and protozoa. Bacterial antigens are usually not available for specific serological tests. Only direct evidence for these infections can be used. The history of infection as reported by the patient has proven to be quite unreliable in most cases and is only used as general information.

The majority of initial serological studies are conducted with the use of the complement fixation method. All tests are reproduced completely and a minimum of 90% agreement within twofold variation is required. All sera showing significant change in antibody, together with any sera which did not reproduce, are tested a third time. For more specific testing or confirmation of these results the Hemagglutination Inhibition and Neutralization methods can be used. These latter serological procedures are very specific and are also employed for follow-up testing whenever the initial studies with the complement fixation method suggest the need for further investigation.

Major Findings: A total of 125 complement fixing antigens have been developed. Approximately three-fourths of the antigens have been thoroughly evaluated and are now being applied in routine testing of study sera. The development and maintenance of large quantities (1,000 ml) of satisfactory antigens for 45 viruses is an integral part of the investigation being carried on by the study. The other antigens are receiving intensive developmental work and 20 of these antigens are under test for specificity. Specific control antisera have been prepared for 85 microorganisms. In addition, to provide improved safety, extensive work has been conducted on the inactivation of the live virus antigens.

The serological studies are being conducted in accordance with three major study designs:

First is the epidemiological studies to determine the frequency of virus experience among study populations. Specimens from representative patients at study hospitals are being tested for evidence of antibody. By studying these specimens, it is possible to establish the frequency of antibody and change in antibody titer to each virus. The data for each hospital is then analyzed in relation to other information from the Collaborative Perinatal Study, and in relation to other information from epidemiological data concerning the seasonal occurrence of abnormal pregnancies and children.

The second and most active category of study involves the selection of particular microorganisms for intensive testing. Studies of this type have involved, for example, the testing of sera from a large number of patients for antibody to toxoplasmosis or rubella. Intensive studies are now being conducted utilizing antigens for Influenza A, Mumps, Cytomegalovirus, Herpes Simplex, and Rubella. Patients identified as having serological evidence for an infection are then grouped and clinical data for these groups and the remaining patients and their children are compared and analyzed.

Third, studies are designed to obtain maximum data concerning the virus experience of patients with abnormal pregnancy outcomes, and "matched control." The results of this type of study are then analyzed in terms of differences in frequency of antibody and antibody change among the abnormals and matched controls. The matching of the patients include factors which are known to influence virus experience, such as time of the year during which the specimens were obtained, race, age, number of living children in the family, and geographic location of the patients. These studies are conducted when a sufficient number

of abnormals of a particular type have been identified so that statistical analysis might establish valid information. The initial studies were directed at abnormalities which are relatively frequent, such as abortions, stillbirths, and neonatal deaths. The less frequent abnormalities or those which cannot be recognized in infancy or early childhood are being studied as greater numbers of these patients are identified in the Collaborative Study population.

Collaborating Studies: The primary deficiency of data in the Study has long been recognized as the late registration of Study patients. Since only 20% of the patients register during the first trimester of pregnancy, it is impossible to document adequately the infectious diseases experience of patients during the first trimester. To provide data on the first trimester of pregnancy, two additional Collaborative Studies were joined with the program of the Section on Infectious Diseases. These are:

1. Study of Viral Infections in Pregnancy
   Dr. Margaret Jones, UCLA and
   Kaiser Hospital in Los Angeles, California

2. Study of Infections in the First Three Months of Pregnancy
   Dr. Robert McCallum
   Kaiser Hospital
   Honolulu, Hawaii

In addition to these studies, the collaboration with the Perinatal Study in the Kaiser Hospital in Oakland with Dr. Yerushalmy has been an integral part of the program since its initiation in 1959.

Significance to the Program of the Institute: The use of micro serological techniques for a large group of new viruses provides an opportunity to investigate the course of human disease caused by viruses which are either difficult to isolate or are resistant to evaluation because the clinical effects are delayed until a long time after infection has subsided. This is particularly true in the case of birth defects. The application of this tool of analysis is providing valuable information on the epidemiological aspects of virus infections.

Proposed Course of the Project: The serological program will be expanded in terms of antigenic materials and the collection of sera. New study arrangements for investigation of viral and genetic abortions have been developed with collaborating groups.

As additional abnormal pregnancy outcomes are reported, these will be added to existing studies on abortions, stillbirths, neonatal deaths, and congenital malformations.

The initial "leads" obtained by the present serological testing are being explored in detail with the use of expanded serological investigations as well as other techniques of virology. It is clear that supplemental sampling is

necessary for patients who register early in the first trimester of pregnancy and for those who have had repeated abnormal pregnancies. Arrangements have been developed for obtaining full sets of serum specimens and data for patients who abort or have stillbirths. Specimen collection for the virus studies has been expanded to include tissue samples from placentas, abortuses, stillbirths, and neonatal deaths so that direct isolation of viral agents is included and extend the serological findings.

Honors and Awards: None

Publications: Sever, J.L.: Rubella as a Teratogen. In Woollam, D.H.M. (Ed.): Advances in Teratology. New York, N.Y., Lagos Press Ltd., 1967, Vol. II, pp. 127-138.

Reed, D., Brown, G., Merrick, Rosalie, Sever, J., and Feltz, E.: A Mumps Epidemic on St. George Island, Alaska. JAMA, 199: 967-971, Mar. 27, 1967.

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Sever, J.L., and White, L.R.: Intrauterine Viral Infection. Ann. Rev. Med. 19, 1968.

White, L.R., and Sever, J.L.: The Role of Infection. In Rubin, A. (Ed.): Handbook of Congenital Malformations. W.B. Saunders, Philadelphia, 1967, pp. 353-364.

Sever, J.L., Reed, D., Kurtzke, J.F., Huebner, R.J., and Kurland, L.T.: A Note on Virus Antibodies in Patients with Multiple Sclerosis. In Alter, M., and Kurtzke, J.F. (Eds.): The Epidemiology of Multiple Sclerosis. C.C. Thomas, Springfield, Ill., 1968, Chapter VIII, pp. 107-109.

Sever, J.L.: Perinatal Infections Affecting the Developing Fetus and Newborn. Conference on the Prevention of Mental Retardation Through the Control of Infectious Diseases. Supported by National Institute of Child Health and Human Development. U.S. Department of Health, Education, and Welfare, Public Health Service Publication No. 1692, Washington, D.C. U.S. Government Printing Office, 1968, 392 pp.

Sever, J.L.: Effects of Virus on the Developing Fetus. In Barnes, A.C. (Ed.): Intra-uterine Development. Philadelphia, Pa., Lea & Febiger, 1968, Chapter 21, pp. 404-418.

Serial No. NDB (CF)-61 PR/ID 835
1. Perinatal Research Branch
2. Section on Infectious Diseases
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Clinical Investigations in Human Volunteers and other Populations of Virus Effects and Production of Prototype Human Antisera and Vaccines.

Previous Serial Number: Same

Principal Investigators: Dr. John L. Sever, PRB, NINDB
Dr. Stephen A. Schacher, CDC
Dr. Gary L. Gitnick, PRB, NINDB
Dr. Robert J. Huebner, NIAID

Other Investigators: Dr. David A. Fuccillo, PRB, NINDB

Cooperating Units: Laboratory of Infectious Diseases, NIAID
National Communicable Disease Center, Atlanta, Georgia
NINDB, Epidemiology Branch (Dr. Jacob Brody)
Bureau of Prisons, Department of Justice (Dr. Myrl Alexander, Director)
Petersburg Federal Reformatory (Dr. Paul Levitt, Chief Medical Officer)

Man Years:

Total:	2.5
Professional:	.5
Other:	2.0

Project Description:

Objectives: To study the efficacy of prophylactic and therapeutic materials for the prevention and control of infectious diseases. To study the safety, antigenicity, communicability, and immunogenicity of candidate rubella vaccines.

Methods Employed: Human volunteer studies are conducted in collaboration with the Federal Bureau of Prisons. These studies are reviewed and approved by the Clinical Research Committee and the Medical Board of the National Institutes of Health, and the Vaccine Development Board of the National Institute of Allergy and Infectious Diseases.

Major Findings: Volunteer studies were initiated to evaluate the safety, immunogenicity, and communicability of lyophilized enteric coated capsules of the HPV-77 live attenuated rubella vaccine. Additional studies with Gilchrist P-48 are in progress.

Significance of the Project: Volunteer studies provide the basic data necessary to evaluate potential rubella vaccines. These studies provide important and necessary information on the effectiveness and safety of such preparations.

Proposed Course of the Project: Additional studies are necessary to evaluate several candidate vaccine strains which are available or shortly will be available. On the basis of these studies the most suitable candidate vaccine strain for large scale testing can be determined.

Honors and Awards: None

Publications: Schacher, S.A., Fuccillo, D.A., Gitnick, G.L., Sever, J.L., and Huebner, R.J.: Oral Administration of Attenuated Rubella Virus Vaccine (HPV-77): A negative report. J. Pediat. 72:2, 255-256, Feb., 1968.

Gitnick, G.L., Fabiyi, A., Fuccillo, D.A., Crockett, P., and Sever, J.L.: Growth of rubella virus in the presence of serum substitutes. Appl. Microbiol. 16:2, 430-432, Feb., 1968.

Serial No. NDB (CF)-62 PR/ID 972
1. Perinatal Research Branch
2. Section on Infectious Diseases
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Experimental Animal Tissue Culture, Histopathological and Serological Investigations of the Role of Viruses and Other Microorganisms in the Perinatal Period.

Previous Serial Number: Same

Principal Investigators: Dr. William T. London, PRB, NINDB
Dr. Gary Birnbaum, PRB, NINDB
Dr. Jack D. Singer, NICHD
Dr. John L. Sever, PRB, NINDB

Other Investigators: Dr. David Madden, NIAID
Mrs. Anita Ley, PRB, NINDB

Cooperating Units: Laboratory of Infectious Diseases, NIAID
University of California (Dr. Margaret H. Jones)
National Naval Medical Center

Man Years:

Total:	4.2
Professional:	1.2
Other:	3.0

Project Description:

Objectives: The infection of gravid and non-gravid animals of several different species by oral and all parenteral routes with various viruses and other microorganisms to determine the effects of these agents on the animals and their fetal tissues.

Attempt to recover inoculated agents from the various animals and fetal tissues and the correlation of these reisolations with time (in gestation) of inoculation, route of inoculation, and dosage given.

Correlate these findings with gross and histopathological findings.

Correlate all of this information with serological findings.

Attempt to isolate infectious agents from urine of 500 day-old human infants and investigate any isolations with possible correlation of any defects found in the children.

Attempt to isolate infectious agents from human abortion tissue.

Methods Employed: An investigation of the role of viruses and other microorganisms in the perinatal period by the continual use of experimental animals; tissue culture techniques; histopathological studies; and serological testing.

Pregnant and non-pregnant animals of various species including monkeys are being inoculated by various routes with viruses and other microorganisms. These animals are being observed and checked for evidence of diseases and/or effects on fetal tissues.

Virus isolation investigations utilizing tissue culture techniques to study the location of virus infection produced and to recover viruses from tissues of experimental animals, human infant urines and human abortive tissue.

Histopathological studies are conducted on specimens obtained from the experimental animal studies.

Extensive serological studies are conducted with the many viral antigens developed for the Collaborative Study and new antigens with materials being studied previously mentioned.

Tissue culture techniques are utilized in the virus isolation investigations of urine collected from day-old human infants.

In conjunction with the Unit on Cytogenetics and with Dr. Jones' group in California, tissue culture techniques and mouse inoculation are utilized in attempts to isolate viral agents and other microorganisms from human abortive tissue.

Major Findings: Animal investigations with pregnant monkeys inoculated intravenously with tissue culture grown rubella virus early in pregnancy have not demonstrated interference with gestation. Neutralizing antibodies developed in all inoculated animals. Virus was recovered from the infected animals from the seventh day through the sixteenth day post inoculation. Vaccine strains have not been transmitted accross the placenta.

Cytomegalovirus has been isolated from the urine of human infants and further studies are being carried out on these infants.

Mycoplasma has been isolated from several specimens of human abortive tissue as well as serologically positive titers for toxoplasmosis on sera from mice inoculated with the abortive tissue.

Significance to the Program of the Institute: A program using experimental animals, tissue culture techniques, and histopathological investigations complements the strict serological approach being used on human sera obtained from the Collaborative Study and thus balances the investigations of the role of viruses and other microorganisms in the perinatal period. It presents the

direct means of investigation of these agents which may contribute to perinatal pathology.

Proposed Course of the Project: Further studies of experimental rubella in day-old monkeys is in progress. Teratogenic studies have been started with cytomegalic inclusion virus, herpes simplex, and mycoplasma. These agents have been injected into pregnant monkeys and studies are being carried out. Cytomegalovirus (mouse) has been injected into pregnant mice to study the teratogenic effect of this virus in mice. Teratogenic studies with the high passage rubella virus (HPV-77) will be completed, examination of the newborn infant monkeys and serological studies finished to see if neutralizing antibodies were stimulated by this high passage material.

The isolation of viral agents from human day-old infant urine will be completed, as will the microorganism isolation from human abortive tissue. Serological studies of patients from which any isolations are made will be carried out to completion.

Honors and Awards: None

Publications: Hildebrandt, R.J., Sever, J.L., Margileth, A.M., and Callagan, D.A.: Cytomegalovirus in the Normal Pregnant Female. Amer. J. Obst. Gynec. 98:8, 1125, Aug. 15, 1967.

Sever, J.L.: Rubella and Other Agents as Teratogens, Status of Research and Prevention. Probleme der Verhutung von Viruserkrankungen. Springer-Verlag, Heidelberg, Germany, 1967, pp. 189-195.

Serial No. NDB (CF)-65 PR/ID 1238
1. Perinatal Research Branch
2. Section on Infectious Diseases
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Chromosomal Studies and Isolation of Infectious Agents from Tissues

Previous Serial Number: Same

Principal Investigators:
Dr. Jack D. Singer, NICHD
Dr. W.T. London, PRB, NINDB
Dr. John L. Sever, PRB, NINDB
Dr. Robert J. Huebner, NIAID
Dr. Roselyn Kolodny, NICHD

Other Investigators:
Dr. Ken Sell, Naval Medical Research Institute, Tissue Bank
Dr. R. McCallum, Kaiser Permanente Foundation Hospital, Honolulu, Hawaii
Dr. David Fuccillo, PRB, NINDB
Renee G. Traub, PRB, NINDB
Anita C. Ley, PRB, NINDB
Flora W. Moder, PRB, NINDB
Pernell Crockett, PRB, NINDB
Mary Ruth Gilkeson, PRB, NINDB

Cooperating Units:
NICHD
National Naval Medical Center, Department of Obstetrics and Pathology (Dr. Lonergan)
Naval Medical Research Institute, Tissue Bank
Kaiser Permanente Foundation Hospital, Honolulu, Hawaii
Laboratory of Infectious Diseases, NIAID

Man Years:

Total:	3.5
Professional:	1.5
Other:	2.0

Project Description:

Objectives: To conduct studies of the chromosomes of aborted and term fetal tissues and to utilize new techniques for the isolation of infectious agents from fetal and adult tissues as combined efforts to obtain direct information on the causes of abnormal pregnancy and pathologic findings.

Methods Employed: Tissue specimens from fetuses and adults are being obtained from collaborating institutions and physicians. Cultures of peripheral leukocytes and tissue cultures are being employed to establish the karyotypes of the abortuses and of the family members. Viral and mycoplasma cultures of the abortus tissues and viral-specific serological tests are also being done.

Major Findings: Mycoplasma has been isolated from a number of the abortus specimens. Recent reports indicate mycoplasma infection may induce alterations of sensitivity of cell cultures to viral infection and produce chromosome damage similar to that described as being induced by viruses in cell and blood cultures.

Significance of Biomedical Research and the Program of the Institute: This study will not only provide a better understanding of the pathology of growth disturbances in fetal life, but will also be of practical value in adding to our basic knowledge in the relationship of virus infections to the development of chromosome abnormalities.

Proposed Course of the Project: Investigations are continuing on the role of viruses as well as mycoplasma infection in relation to chromosome abnormalities in early spontaneous human abortion.

Awards and Honors: None

Publications: None

Serial No. NDB (CF)-66 PR/ID 1326
1. Perinatal Research Branch
2. Section on Infectious Diseases
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Rubella Vaccine Development Program

Principal Investigators: Dr. John L. Sever, PRB, NINDB
Dr. Gary L. Gitnick, PRB, NINDB
Dr. David Fuccillo, PRB, NINDB
Dr. Akinyele Fabiyi, PRB, NINDB
Dr. Carrie Whitmire, Microbiological Associates, Bethesda, Maryland
Dr. James C. Overall, NICHD
Dr. Stephen A. Schacher, CDC
Dr. Robert J. Huebner, NIAID

Other Investigators: Renee Traub, PRB, NINDB
Flora Moder, PRB, NINDB
Pernell Crockett, PRB, NINDB

Cooperating Units: Laboratory of Infectious Diseases, NIAID
Vaccine Development Branch, NIAID (Dr. Daniel Mullally)
NICHD
CDC
Microbiological Associates, Bethesda, Md.

Man Years:

Total:	4.1
Professional:	2.1
Other:	2.0

Project Description:

Objectives: Collaborate with the Vaccine Development Branch, NIAID, in studies on the development of live attenuated and inactivated rubella virus vaccines. Provide project surveillance for contracts awarded by the National Institutes of Health for rubella vaccine work. Provide intramural guidance, support, competence, and laboratory studies as well as conduct volunteer studies in conjunction with this program.

Methods Employed: The intramural program has undertaken basic laboratory studies aimed at the development of candidate live attenuated rubella vaccine strains and at the development of potential inactivated vaccine preparations. Temperature adaptation studies have been performed and studies aimed at the adaptation of the HPV-77 attenuated rubella strain and a number of other candidate rubella vaccine strains, to avian tissue culture systems have been

performed.

The Vaccine Development Branch, NIAID, is supporting 10 contracts relating to research on the development of rubella vaccines. Eight contracts are with major pharmaceutical manufacturers and two are materials and services, research and support contracts.

For this program, contract Project Officers are assigned from the Section; reference specimens, sera, and testing is provided; experimental animal studies are conducted; and volunteer studies are performed with candidate materials.

All studies are conducted in conjunction with the Vaccine Development Program, NIAID.

Major Findings: Rubella virus CF and HA antigens have been produced employing BHK-21 monolayer cell cultures. Methods have been developed for the continuous and concurrent production of rubella virus and CF antigen in suspension cultures with daily harvests in excess of two months.

Antigens have been chromatographed on Sephadex G200 columns and have been treated with proteolytic and nucleic acid destroying enzymes. A single HA antigen and CF antigen from untreated and aqueous phase ether treated cell pack material have been demonstrated and shown to be sensitive to trypsin but not to DNase and RNase. Sedimentation studies have demonstrated the presence of nonsedimentable aqueous phase complement fixing antigen and a sedimentable emulsion phase complement fixing antigen. Several attenuated rubella virus strains have been successfully adapted to avian tissue culture systems. Attenuated rubella virus strains have been lyophilized, encapsulated, and administered orally to monkeys. Interferon characterization studies employing both the yield reduction method and the placque reduction method have demonstrated that several strains of rubella virus produce high levels of interferon. Placque assay techniques for rubella in RK-13 cells, RK-1 cells, and rabbit cornea cells have been developed. Human serum albumin has been shown to act both as a serum substitute and as a stabilizer for rubella virus.

Pools of the HPV-77 attenuated rubella virus strain have been prepared in African green monkey kidney tissue culture, and in canine kidney tissue culture. These pools have been safety tested and will shortly be administered to human volunteers. Inactivation studies using formalin, ultraviolet, and beta-prone are in progress.

Significance of the Project: An effective and a safe live attenuated rubella vaccine for the immunization of children and an inactivated rubella vaccine for the immunization of women of child bearing age would eliminate the fetal damage caused by this infection.

Proposed Course of the Project: The rubella vaccine development program will continue to develop and evaluate candidate live attenuated rubella vaccine preparations and inactivated rubella vaccine preparations. Expanded testing

of candidate, live, attenuated, injectable vaccines; candidate oral vaccines; and inactivated subparticle vaccines will be continued in our laboratories and in the volunteer program at the Petersburg, Virginia Federal Reformatory.

Honors and Awards: None

Publications: Fabiyi, A., Gitnick, G.L., and Sever, J.L.: Chronic Rubella Virus Infection in the Ferret (Mustela putorius fero) Puppy. Proc. Soc. Exp. Biol. Med. 125:766, Jul. 1967.

Serial No. NDB (CF)-67 PR/ID 1502
1. Perinatal Research Branch
2. Section on Infectious Diseases
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Immunological Studies of Virus Infections in Experimental Animals and Man

Previous Serial Number: None

Principal Investigators: Dr. Akinyele Fabiyi, PRB, NINDB
Dr. Teresita S. Elizan, PRB, NINDB
Dr. Gary L. Gitnick, PRB, NINDB
Dr. John L. Sever, PRB, NINDB
Dr. William London, PRB, NINDB

Other Investigators: Dr. D.A. Fuccillo, PRB, NINDB
Pernell W. Crockett, PRB, NINDB
Flora Moder, PRB, NINDB
Mary Ruth Gilkeson, PRB, NINDB

Collaborating Institutions and Investigators:

1. National Institute of Allergy and Infectious Diseases
   a. Laboratory of Infectious Diseases - Dr. Robert J. Huebner
   b. Vaccine Development Branch

2. Philadelphia General Hospital, Philadelphia, Pa.
   Department of Neuropathology - Dr. Lucy Rorke

3. Georgetown University School of Medicine, Department of Pediatrics, Washington, D.C. - Dr. Philip Calcagno, Dr. Tatiana Antonovych

4. Microbiological Associates, Inc., Bethesda, Md. - Mr. M.M. Vincent

5. Cutter Laboratories, Inc., Berkeley, California - Dr. Karl Hok, Dr. Robert E. Louie

Man Years:

Total:	5.0
Professional:	1.0
Other:	4.0

Project Description:

Objectives: To explore the nature of the interactions between viruses and their hosts in tissue culture systems, experimental animals and man, with

emphasis on the study of resistance mechanisms, especially those concerned with the development of specific immunity associated with either circulating or cell associated antibodies. To elucidate the basic immunochemical structure of viruses and virus reactions by biological, biochemical, and biophysical methods. To develop, prepare, and concentrate virus reagents for serologic identification of virus and virus induced products. To determine the susceptibilities of experimental animals to virus infections and follow the course and development of virus antigens with concomitant antibody production, pathology of infections in suckling adult and gravid animals and the effect on the fetus and the newborn. To develop and prepare inactivated virus vaccines suitable for prevention of virus diseases.

Methods Employed: Growth characteristics at different temperatures and pH's, reaction to chemical and physical agents, physical characteristics such as sedimentation coefficient and buoyant density using sucrose gradient and high speed centrifugation were evaluated in tissue culture systems in combination with serological methods including complement fixation and neutralization tests, and hemagglutination inhibition. Techniques were developed for the preparation, concentration, continuous production of virus reagents in tissue culture; methods for the identification of virus and virus products in susceptible hosts including radioisotope precipitin test, direct CPE neutralization tests were carried out in tissue culture systems. Adult and newborn animals were inoculated by different routes. These animals were examined for their reactions to virus infections. Chronic virus infection, antibody production, pathology, virus pathogenesis were studied in suckling animals. The effect of virus infection on gravid animals and on the fetus and newborn were evaluated. Inactivated virus vaccines were prepared from viruses grown in tissue culture and their immunogenic reactions and levels of protective antibodies were evaluated in tissue culture systems, by serological methods including CF, HI, and neutralization tests.

Major Findings: Virus Growth Characteristics: Using rubella virus as a model, virus infectivity titers at temperatures below 37° C were higher when virus infected cells were incubated at between 29 - 34° C with the pH of the maintenance medium adjusted to pH 6.6.

Virus Reactions to Chemical Agents: Beta-propiolactone, formalin and ether were found to be deleterious to rubella virus. At a concentration of 1:4000 for one hour at 4° C, beta-propiolactone destroyed virus infectivity and immunogenicity; while the same concentration of formalin at 4° C for one hour did not affect appreciably virus infectivity or immunogenicity. Treatment of virus for 5 minutes with ether destroyed virus infective properties.

Virus Serologic Reagents:

(a) Sedimentable and non-sedimentable CF antigens

Treatment of rubella virus with ether resulted in the production of specific sedimentable and non-sedimentable (soluble) complement fixing antigen preparations which were serologically indistinguishable. Prolonged, repeated or

treatment of crude antigen at pH 9.0 resulted in increase in the CF titer of the soluble antigen. These antigen preparations could be concentrated to any desired volume. They were also found to induce specific neutralizing and HI antibodies in experimental animals.

(b) Continuous and Concurrent Production of Virus Antigen and Infectivity:

Rubella virus CF antigen and infectious virus were produced continuously and concurrently for as long as 63 days in suspension cultures. Maximum observed CF titer was 1:32, while peak infectivity titer was greater than 8 $\log_{10}$/ml. The continuous production of CF antigen and virus infectivity persisted when cell cultures which have been frozen for as long as 6 months were replanted as monolayer cultures.

(c) Virus Growth in Media with Additives

Infected tissue culture cells maintained with media supplemented with either serum, injectable human albumin, or cholesterol supported rubella virus growth. Human serum albumin proved to be the best substitute for serum. Such a preparation will be of immense value in the preparation of vaccines for human use in order to fulfill the requirements of DBS for human vaccines.

Experimental Animal Studies:

(a) SV_{40} Virus Infection in African Green Monkeys:

Normal African green monkeys infected by the intravenous injection of SV_{40} virus developed systemic virus infection. High virus titers were obtained from the spleen and kidney cortex two days post infection. At two weeks post infection, however, the kidney medulla had the highest virus titer, while that in the kidney cortex had diminished considerably. Viremia was limited to the first week post infection, while viruria ran parallel with the finding and increase in virus titer in the kidney medulla. Results of clinical pathologic findings suggest possible renal damage resulted from SV_{40} infection.

(b) Chronic rubella virus infection in ferrets:

The infection by different routes of newborn ferret puppies with rubella virus resulted in chronic virus infection which lasted up to 8 weeks and in those puppies infected by the intracranial route for 12 weeks. In 3 of 36 puppies inoculated by the IC route, corneal cloudiness with microblepharon was observed 6 weeks post infection. Highest virus titer was found in animals inoculated by the IC route. Furthermore, animals inoculated by the IC route shed virus longer and at 33 days post infection showed significant brain lesions confined to the striking alterations in blood vessel structure. These changes included thickening of the endothelium with swelling and fragmentation. Some vessels showed elevation and folding of the elastic lamina with some thickening of the wall. These results are similar to those observed in congenital rubella in human infants and suggest that the suckling ferret could be a useful model for the study of the pathogenesis and prevention of rubella.

Significance of These Studies: Considerable amounts of effort and energy are being directed to the development of a suitable and effective vaccine for one of the viruses known to cause mental retardation, and other neurological and sensory disorders of infancy and childhood. In the course of these studies considerations have to be given to problems of virus purity, concentration, identification and characterization of virus strains and the immunogenicity of vaccines, together with the immunological reactions in man induced by virus infections. The approaches described in this report are basic and are essential tools for understanding and solving some of the problems usually encountered, and those which will occur in the studies of resistance mechanisms, especially those concerned with the development of immunity and resistance to infections.

Proposed Course of the Project: There are many uncertainties which still require further examinations. Tissue susceptibility, site of virus implantation, the progressive course of virus multiplication in susceptible experimental animals need to be investigated exhaustively. Some tools for these studies include the use of fluorescent antibody tests for pathogenesis, while more pathology will give a better picture of the nature of the etiologic agent. Some of the reactions of virus to chemical and physical agents and the immunogenicity of inactivated agents to produce some form of protection to the disease are as yet not clearly understood. The biophysical, biochemical and biological properties of viruses which will aid in shaping the understanding of why certain viruses behave in certain ways in susceptible hosts (tissue culture and animals) and why some are more immunogenic than others, while others need more protein mass to induce immunity, still require more extensive examination. Tools for such studies include electron-microscopy, biochemical and biophysical methods, radioisotope specific tests, and more animal studies. When these have been accomplished and enough information becomes available, and armed with this knowledge, it would be possible and be more feasible to combat and control infectious agents, especially those of virus origin which are slow growing and have been implicated as causes of disorders of the nervous system and congenital malformations.

Honors and Awards: None

Publications: Fabiyi, A., Calcagno, P.L., Sever, J.L., Antonovych, T., and Wolman, F.: Isolation of SV_{40} virus and its effect on renal function in African green monkeys. Nature. 215:5096, 88-89, Jul. 1967.

Serial No. NDB (CF)-67 PR/ID 1503
1. Perinatal Research Branch
2. Section on Infectious Diseases
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Epidemiologic Studies of Perinatal Infections

Previous Serial Number: None

Principal Investigators: Dr. John L. Sever, PRB, NINDB
Dr. Jane Todaro, PRB, NINDB
Dr. James C. Overall, NICHD

Other Investigators: Dr. David Fuccillo, PRB, NINDB
Anita Ley, PRB, NINDB
Renee Traub, PRB, NINDB
Dr. Gordon Avery, Children's Hospital of the D.C.
Dr. Sheldon Korones, Memphis, Tennessee
Dr. Richard Asofsky, NIAID
Dr. Paul Alepa, Georgetown University School of Medicine

Cooperating Units: NICHD
Children's Hospital of the D.C.
Child Development Study, Memphis, Tennessee - affiliated with the Perinatal Research Study and the University of Tennessee
NIAID
Georgetown University School of Medicine

Man Years:

Total:	4.1
Professional:	1.1
Other:	3.0

Project Description:

Objectives: To utilize information from the Collaborative Perinatal Research Study to identify pregnancies complicated by maternal infections; to further delineate these cases by serologic testing of the stored sera; to utilize Collaborative Study data to determine outcome of these pregnancies in relation to the outcomes of matched controls and the general study population in order to gain information on the frequency of maternal infections during pregnancy and their effects on the developing fetus.

To investigate the immunologic consequences of maternal and fetal rubella virus

infection during pregnancy. To utilize special immunologic techniques to determine the frequency of antiglobulin activity in maternal sera during pregnancy following maternal rubella and to investigate serum immunoglobulins, antibodies and lymphocyte-associated immune mechanisms in infants with the expanded congenital rubella syndrome.

Methods Employed: Computer identification of Collaborative Study pregnancies complicated by maternal infection. Individual review of maternal charts and serologic testing of sera to define the nature of the alleged illness and the certainty of the diagnosis. "Blind" review of the pediatric charts of "case" and "control" pregnancies. Tabulation and comparison of development and illness data.

Testing of serum obtained at delivery from mothers having rubella during pregnancy for antiglobulin activity (Dr. Alepa).

Controlled observation of congenital rubella syndrome and control infants after routine immunization procedures. Testing of lymphocytes (Dr. Leikin) and serum (Dr. White, Mrs. Ley, Dr. Asofsky) before and after immunization for immunoglobulin and antibody levels.

Major Findings: Among 30,059 pregnancies studied by the Collaborative Perinatal Research Study, 1958-1964, there were 46 illnesses diagnosed as mumps (M), 23 as varicella (V), and 11 as rubeola (R). Tests on frozen, stored maternal sera substantiated the diagnosis in 34 (M), 15 (V), and 2 (R) cases. The pediatric outcomes of these serologically substantiated cases and 90 matched controls were reviewed and abstracted by professional personnel. Maternal mumps was associated with a tendency toward small head size; birth weight and length distributions were not appreciable different from controls. Three of the infants had hyperbilirubinemia of unknown etiology. Two others had persistent hepatomegaly. An enlarged liver was repeatedly observed in one child who was hospitalized at age 15 months with diabetic acidosis. Mental retardation was strongly suspected in 2 additional cases while a third was microcephalic. Another child was apparently normal until age 3 months when she died after a 12 hour illness; the autopsy showed gastroenteritis and interstitial pneumonia thought to be of viral origin. In the varicella group (15 cases) there were 2 instances of hyperbilirubinemia of unknown cause. One infant (whose mother had the infection at delivery) developed neonatal varicalla and was mentally retarded at 1 year of age. Both of the children whose mothers had rubeola during pregnancy were normal. Among the controls, 6% had hepatomegaly and 2% had hyperbilirubinemia. There were no cases of death, diabetes, microcephaly or mental retardation.

Among these 30,059 pregnancies (occurring prior to the 1964 rubella epidemic) there were 25 serologically substantiated cases of maternal rubella occurring during the course of pregnancy. The frequency of clinical maternal rubella during non-epidemic years was thus defined as approximately one per 1000 pregnancies. Twenty per cent of the children resulting from these pregnancies had two or more of the "new" features of the expanded congenital rubella syndrome. This indicates that the expanded congenital rubella syndrome did occur prior

to 1964 and cannot be attributed to a supervirulent mutant virus. Sixteen per cent of the patients had micrognathia; in each case this was seen in an infant with two or more of the features of the expanded congenital rubella syndrome. Orthopedic abnormalities were also observed in 16 per cent of the infants, also in babies having two or more of the features of the expanded congenital rubella syndrome. It is suggested that these two features may represent true manifestations of congenital rubella.

Mothers infected with rubella during the course of pregnancy showed a greater than 3-fold increase in the prevalence of antiglobulin activity in the serum obtained at the time of delivery. This approximates the incidence of anti-globulins after rubella in the non-pregnant adult. No increase in the prevalence of anti-Gm antibodies could be detected and there was no association between the antiglobulin activity and the clinical features of the infant. Cord blood IgM immunoglobulin levels were determined on nine of the infants and were found to be definitely elevated in three cases. Two of the infants whose cord blood possessed elevated IgM levels were essentially normal (one had suspect congenital heart disease), and the third (whose mother had rubella at 30 weeks gestation) had only petechiae and suspect mental retardation.

Studies of immune competence in infants with the congenital rubella syndrome have shown normal systemic and local responses to live rubeola vaccine, vaccinia virus, and DPT. The serum of these infants nearly always contained detectable antibody directed toward rubella virus. After immunization they developed levels of circulating antibody quite comparable to those of normal infants after similar immunization. Serum immunoglobulin levels were consistent with chronic infection: moderately elevated IgM, mildly elevated IgG and variable IgA levels. The prevalences of antibodies to naturally-encountered agents such as E. Coli 075, parainfluenza 3, adenovirus, etc., were only slightly less than those observed in the sera of normal infants. Lymphocyte transformation studies have shown an apparent decrease in antigen-induced bastogenesis at age 1 - 2 years despite normal responses to phytohemagglutinin.

Significance of the Project: The studies relating to possible adverse effects of maternal mumps and varicella were carried out on the "first half" of the Collaborative Perinatal Research Study population and were intended as a survey. The data reported allow for the definition of certain hypotheses which may be tested through analyses of the "second half" of the population when those data are available.

The studies of immune competence in congenital rubella indicate a dissociation between the capacity for recovery from infection and the acquisition of circulating antibodies. The lymphocyte transformation studies suggest an association of chronic infection with abnormal lymphocyte function. These observations define areas of immune ontogeny which need to be investigated in order to better understand the pathogenesis of perinatal infections. Techniques of specific antigen-induced lymphocyte transformation, lymphocyte preservation in liquid nitrogen, and interferon product have been developed which will be useful in this regard.

Proposed Course of the Project: Further epidemiologic studies using data from the Collaborative Perinatal Research Study will be undertaken.

Studies will be undertaken to define the consequences of infections during neonatal and infant life. These will utilize primarily experimental animals and clinical data from the Collaborative Perinatal Research Study.

Immune ontogeny will be further investigated in normal and abnormal humans and cells therefrom as well as in experimental animals.

Honors and Awards: None

Publications: None

Serial No. NDB (CF)-67 PR/ID 1504
1. Perinatal Research Branch
2. Section on Infectious Diseases
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Experimental Pathology and Neurology of Infections of the Central Nervous System
A. Fluorescent-antibody studies on rubella-infected newborn ferrets

Previous Serial Number: None

Principal Investigators: Dr. Teresita S. Elizan, PRB, NINDB
Dr. Akinyele Fabiyi, PRB, NINDB
Dr. John L. Sever, PRB, NINDB
Dr. William London, PRB, NINDB

Other Investigators: K. Buchler, PRB, NINDB
P. Crockett, PRB, NINDB

Man Years:

Total:	2.0
Professional:	1.0
Other:	1.0

Project Description:

Objectives: To study the pathogenesis of rubella infection in newborn ferrets with specific emphasis on the brain, using fluorescent-antibody techniques, histopathology, and neurological evaluation.

Materials and Method: Studies of rubella infection in newborn ferrets are now in progress. Newborn ferret puppies, 1 - 2 days old, are inoculated intracerebrally with 0.02 ml of rubella virus. Uninoculated puppies of the same age are used as controls. The animals are sacrificed at serial intervals post-inoculation: 1 hour, 2 hours, daily from day 1 (24 hrs.) to day 14, weekly from third week to eighth week. Two to four infected puppies and corresponding controls will be used at each autopsy date. The brain, heart, lungs, kidney, liver, and spleen are taken for fluorescent-antibody study, routine histology, and virus isolation in tissue cultures.

The preparation of reagents and materials for FA work includes DEAE and Sephadex column procedures, and various immunodiffusion and immunoelectrophoretic studies. The more immediate tissue preparation, storage, and staining techniques are the conventional ones used in the indirect FA test.

Results (January - April, 1967): Normal and hyperimmune (to rubella) monkey sera (obtained from Abbott Laboratories), and fluorescein-labelled conjugate (goat anti-monkey globulin, obtained from Hyland Laboratories) have been passed through DEAE and Sephadex columns, and characterized on immunoelectrophoresis and immunodiffusion tests.

Brain tissues, and corresponding controls, are being studied for specific fluorescence. Routine neuropathologic studies on three 6-day post-inoculation brain tissues, and four 42-day post-inoculation brain tissues did not show any significant changes.

Problems and Proposed Course of the Project: The availability of experimental animals remains a major problem. To implement the proposed schedule of autopsies at serial intervals post-inoculation, a minimum of 88 puppies (2 infected and 2 control puppies on 22 autopsy dates) are being inoculated with rubella virus.

The quality of commercial conjugates available leaves much to be desired. It may be imperative to make one's own conjugate, despite further investment in time and effort.

Problems inherent in the technique itself and in the particular tissues one is working on can only be recognized and remedied as more experience in the test is acquired.

The pathogenesis of rubella infection, especially in the central nervous system, is obviously important, and a sensitive test like the fluorescent-antibody technique should give some answers. The study will be continued and expanded as more experimental animals are available.

Honors and Awards: None

Publications: None

Serial No. NDB (CF)-67 PR/ID 1505
1. Perinatal Research Branch
2. Section on Infectious Diseases
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Experimental Pathology and Neurology of Infection of the Central Nervous System
B. The pathogenesis of mouse cytomegalovirus infection by fluorescent-antibody technique

Previous Serial Number: None

Principal Investigators: Dr. Teresita S. Elizan, PRB, NINDB
Dr. W.T. London, PRB, NINDB
Dr. John L. Sever, PRB, NINDB

Other Investigators: Kris Buchler, PRB, NINDB
Pernell Crockett, PRB,NINDB

Man Years:

Total:	1.0
Professional:	.5
Other:	.5

Project Description:

Objectives: The pathogenesis of cytomegalovirus infection in the mouse will be studied by fluorescent-antibody technique, routine histopathology, and virus isolation. Emphasis will be on the central nervous system, liver and kidney.

Materials and Methods: The initial phase of the study, i.e., virus isolation and titration preceding fluorescent microscopy, has been conducted by Dr. London, and it will be discussed in the companion project, "Cytomegalovirus Hepatitis in the Mouse."

ICR/HA female mice, 7 weeks old (24 to 28 gm.), free of naturally occurring CMV, and the Smith strain of MCMV (from Dr. Donald Henson) are used.

Intraperitoneal inoculation of 0.3 ml virus suspension (undiluted 10^{-1}, 10^{-2}, 10^{-3}, and 10^{-4}) into test animals, and of 0.3 ml salivary gland homogenate prepared from non-infected mice of the same strain into controls was done. Two animals from test and control groups were autopsied at days 1, 4, 6, 10, and 14 and at the fourth and eighth week post-inoculation. Brain, liver, spleen, kidney, lung, and salivary glands were taken for fluorescent microscopy, routine histopathology, and virus titration.

Results: The maximum sublethal dilution of virus inoculum capable of producing focal histopathologic and chronic infection will be determined by the above preliminary study, in addition to Dr. London's project on "Cytomegalovirus Hepatitis in Mouse."

Indirect fluorescent-antibody studies will be done on the organs already collected.

Proposed Course of the Project: Using the optimum dilution of virus as determined in the above preliminary study, the pathogenesis of MCMV infection will be studies—onset, development, chronicity, recovery, status on reinoculation. Special emphasis will be on encephalitic and hepatic changes on fluorescent microscopy. Serial autopsies following inoculation of test animals will be done.

The relevance of the study to human cytomegalic inclusion disease with brain and liver involvement is obvious.

Honors and Awards: None

Publications: None

Serial No. NDB (CF)-67 PR/ID 1506
1. Perinatal Research Branch
2. Section on Infectious Diseases
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Maternal Infection and Pregnancy Outcome

Previous Serial Number: None

Principal Investigator: Dr. David A Fuccillo, PRB, NINDB
Dr. John L. Sever, PRB, NINDB
Dr. Robert J. Huebner, NIAID

Other Investigators: Dr. Gary Gitnick, PRB, NINDB
Renee Traub, PRB, NINDB
Mary Ruth Gilkeson, PRB, NINDB
Flora Moder, PRB, NINDB

Cooperating Units: Laboratory of Infectious Diseases, NIAID
University of California (Dr. Margaret H. Jones)
Hawaii Permanente Medical Group (Dr. Paul F. McCallin)
University of Puerto Rico, School of Tropical Medicine
(Dr. Dolores Mendez-Cashion)

Man Years:

Total:	4.5
Professional:	1.0
Other:	3.5

Project Description:

Objectives: To utilize various virological techniques in an intensive study of viruses to determine their role in the production of birth defects and related abnormalities. To develop virological techniques necessary for the investigation of the natural course of the disease as caused by the infectious agents.

Methods Employed: The standard virus isolation in serum neutralization test were used for the use of large scale testing on the study Pregnant Women and their Children. The development of new techniques such as the HI test and the use of the RK1 direct CP neutralization test help determine the frequency of virus experience among study populations along with the presence of antibody and change in antibody titer to the virus. The RK1 neut test is being used to establish the reliability of the HI test and determine its sensitivity and specificity. A serologic study utilizing these tests on sera collected on the collaborative population during 1966 was conducted to determine the current

susceptibility of pregnant women to rubella. During and following the epidemic of 1964 specimens of the placenta were obtained from a majority of the deliveries. Utilizing this placental material, we are completing the testing of 1500 placentas of rubella virus and for the purpose of identifying children with congenital rubella by the presence of rubella in the placenta material. Many of the defects caused by the material are not obvious in the very young infant and in fact may be seen in the process of developing in the postnatal period. The use of a latex anti-IgM test may prove to be a valuable method to screen for high IgM levels.

Major Findings: Serum specimens were obtained from 500 pregnant women registered during January through April 1966. It was found that there was a significant reduction in the frequency of pregnant women without antibody. 7.8% were found to be susceptible as compared to 17.5% in 1962. At the present time there are more white susceptible patients (10%) than Negro (3.9%). The high susceptibility is no longer highest among the young patients but among women 16 years or over. It would appear that approximately 8% of the pregnant women in this population remain susceptible to rubella. Other studies are directed towards investigation of the prevalence of virus experience in the population under surveilance, also specific studies of infection among patients whose pregnancy determinated in an abnormal outcome are being conducted. Special studies are being directed toward abnormal pregnancy outcome which can be recognized shortly after birth such as abortions, stillbirths, neonatal deaths, and congenital malformations including congenital heart defects. Several viruses have been found to occur in high frequency in specific patients with abnormal pregnancy outcomes. Particular emphasis in the studies relate Coxsackie B Virus. Other viruses which are of interest includes Cytomegalo Virus and Herpes Virus.

Significance of the Program to the Institute: The results from these studies will help determine what effect virus infection has on abnormal pregnancy outcomes, and will also provide valuable information on the epidemiological aspects of virus infections.

Proposed Course of the Project: New study arrangements for investigation of viral infections and their possible effect on the genetic mechanisms and immunological competence are being developed. Other studies will be conducted in cooperation with the several collaborating groups concerning the role of viruses in the etiology of abnormal children.

Honors and Awards: None

Publications: Gitnick, G.L., Vincent, M.M., Auletta, A., Ley, A.C., Tzan, N., and Sever, J.L.: Production of Rubella Hemagglutinating Antigen in Suspension Cultures. Appl. Microbiol. 15:5, 1244-1247, Sept. 1967.

Fuccillo, D.A., Gitnick, G.L., Traub, R.G., Wong, K., Sever, J.L., and Huebner, R.J.: Cultivation of Rubella Virus in Avain Tissue Cultures and Embryonated eggs. Proc. Soc. Exp. Biol. Med. 125:4, 1015-1018, Aug.-Sept., 1967.

Vincent, M.M., Gitnick, G.L., Fabiyi, A., Hensen, S.A., Sever, J.L., and Huebner, R.J.: Rubella Virus: Continuous and Concurrent Production of Complement-fixing Antigen and Infectious Virus in Suspension Cultures. Appl. Microbiol. 15:5, 1198-1201, Sept. 1967.

Serial No. NDB (CF)-65 PR/ID 1270
1. Perinatal Research Branch
2. Section on Infectious Diseases
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Toxoplasmosis: Serological and Clinical Studies.

Previous Serial Number: NDB(CF)-65 PR/PN 1270

Principal Investigator: Dr. John L. Sever, PRB, NINDB

Other Investigators: Dr. Joseph S. Drage, PRB, NINDB

Cooperating Units: Section on Pediatric Neurology, PRB, NINDB

Man Years:

Total:	.4
Professional:	.2
Other:	.2

Project Description:

This study relates rises in antibody titer to abnormal pregnancy outcomes. Within the Pediatric Neurology Section, a hand review was completed on 128 cases that had shown various degrees of titer rise. Within the group of 47 patients with titer elevations of greater than 4096, or significant increases in antibody titer, five were found to have definite toxoplasmosis and ten were suspected of having toxoplasmosis. The ten included six with motor retardation, two pregnancies resulted in stillbirths, and two in neonatal deaths. The sera from ten of the remaining 32 apparently normal children were tested for antibody to toxoplasmosis and one was found to have a high titer. Study in progress awaiting computer analysis.

Honors and Awards: None

Publications: None

Serial No. NDB (CF)-63 PR/OC 1144
1. Perinatal Research Branch
2. Office of the Chief
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: An Instrument For The Conduct Of A Retrospective Study Of Seizures, Cerebral Palsy, Mental Retardation and Other Neurological and Sensory Disorders of Infancy and Childhood.

Previous Serial Number: Same

Principal Investigators: Z.A. Shakhashiri, M.D., PRB, NINDB
Leonard V. Phelps, PRB, NINDB
Glen S. Bartlett, M.D., PRB, NINDB

Other Investigators: Lenore Bajda, M.D., PRB, NINDB
John R. Day, M.D.
Blanche L. Vincent, S.N.O., PRB, NINDB
Zula C. Meekham, B.S.N., PRB, NINDB
Rose R. Tortorella, PRB, NINDB

Cooperating Units: Georgetown University Hospital, Retarded Children's Clinic, Selected Maternity Hospitals and Physicians in Metropolitan Washington

Man Years:

Total:	.35
Professional:	.30
Other:	.05

Project Description:

Objectives: Design an instrument for the conduct of a retrospective study of seizures, cerebral palsy, mental retardation and other neurological and sensory disorders of infancy and childhood in order to test certain basic and important hypotheses concerning the occurrence of neurological damage.

Methods employed: Recognized damaged outcomes of pregnancy, such as seizures, diplegias, hemiplegias and choreoathetoids are to be studied and related to defined perinatal or postnatal events. These outcomes were selected because they were construed to be related to or manifestations of or involved in the biological or psycho-sociological mechanism underlying the following hypotheses: (1) anoxia, (2) toxic influences on the brain, (3) metabolic influences, (4) trauma to the head, (5) infection of the brain, (6) dehydration of the child, (7) genetic or familial patterns and (8) socioeconomic status.

Proposed Course of the Project: The abstraction of the maternity and nursery records and interviewing of the mothers have been completed. The physicians of sib controls have been contacted and information attesting to the health status of these sibs has been obtained. All forms have been edited and coded, and IBM cards have been keypunched. Partial analysis of the data has been carried out, and the remainder will be completed shortly. Termination of the present phase of the study is anticipated by the end of June, 1968. Comparison of findings in this study with findings in the Collaborative Study will be carried out at a later time.

Honors and Awards: None

Publications: None

Serial No. NDB (CF)-63 PR/OC 1146
1. Perinatal Research Branch
2. Office of the Chief
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Public Health Implications Study of Perinatal Mortality in the Collaborative Study and in the Collaborative Study Cities.

Previous Title: Revision and Expansion of Previous Project Entitled A Commentary On The Appropriateness Of The Use Of Certain Tabular Data, For Formulating Generalizations Concerning Populations In The Same Cities As Those In Which The Collaborative Study On Cerebral Palsy, Mental Retardation And Other Neurological And Sensory Disorders Of Infancy And Childhood Is Being Conducted.

Previous Serial Number: Same

Principal Investigators: Z.A. Shakhashiri, M.D., PRB, NINDB
Leonard V. Phelps, PRB, NINDB
Glen S. Bartlett, M.D., PRB, NINDB

Other Investigators: None

Cooperating Units: The Census Bureau and the National Center for Health Statistics cooperated in the furnishing of necessary statistical information for the United States and cities. The respective state or city health departments are providing natality and mortality data for the Project cities.

Man Years:

Total:	0.50
Professional:	0.30
Other:	0.20

Project Description:

Objectives: To evaluate fetal and infant mortality of the Collaborative Study population and of the cities from which that population is drawn, with the aim of comparing the two populations, city by city, and institution by institution, on mortality characteristics.

Methods employed: In addition to the data previously available from the National Center for Health Statistics for perinatal events, detailed data on natality and perinatal mortality are being sought for the study cities from

either the state or city health departments, whichever has jurisdiction for these records. The data include figures for livebirths, stillbirths, and deaths under 24 hours, 1 day to 7 days, 8 days to 28 days and 1 month to 12 months, evaluated by birthweight, length of gestation, race and sex, and plurality for the years 1959 through 1966. Corresponding data will be compiled by institution for the PRB study population. The state or city health departments have been asked to furnish either completed tabulations or raw data to be tabulated (arrangements finalized) by the PRB Section on Data Management and Retrieval.

Considerable effort has been and is being expended, in connection with the Section on Data Management and Retrieval, PRB, and the Office of Biometry, NINDB, to create a usable data file of the external data being obtained in connection with this study. The aim is to provide a file with more general utility than the limited scope of this study. When such a file is created, the information necessary to make use of the file will be made available to interested persons in PRB.

Major Findings: Evaluation of birthweight and length of gestation data for all core live births (first and subsequent pregnancies) reveals differences between races and between sexes that are generally persistent among all the institutions. Birthweights are lighter among non-whites than among whites, and among females than among males. With white males the heaviest, the order of decline is next white female, then, at about the same weight, non-white males, then non-white females. There is a particular excess of non-whites at low birth weights (2500 grams or less). Length of gestation is shorter among non-white than among whites by about 1 week, with an excess of both short-gestation and long-gestation deliveries among non-whites. Length of gestation is slightly shorter among males than among females in both races, but less consistently so among whites.

Perinatal mortality has declined in the study population since its first year, with a transient elevation in 1962. Group I mortality (fetal deaths 1001 grams and over plus deaths under 7 days of age per 1000 total births) declined from 28.5 in 1959 to 17.6 in 1966 (mean 21.7) among whites and from 33.2 to 21.8 (mean 28.4) among non-whites. Group II mortality (fetal deaths 501 grams and over plus deaths under 28 days per 100 total births) declined from 34.9 in 1959 to 19.1 in 1966 (mean 26.0) among whites and from 39.8 to 25.5 (mean 33.3) among non-whites. These trends tended to persist from institution to institution, though to varying degrees.

It is anticipated that the file will be created and the present phase of the study completed by the end of June, 1968.

Honors and Awards: None

Publications: None

Serial No. NDB (CF)-66 PR/OC 1356
1. Perinatal Research Branch
2. Office of the Chief
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: The Association of Maternal Age and Parity to Pregnancy Outcome and to Certain Obstetric Complications.

Previous Serial Number: Serial No. NDB (CF)-66 PR/SA 1356

Principal Investigator: Stewart H. Clifford, M.D.
Boston Lying-In Hospital, Boston, Mass.

Other Investigators: None

Cooperating Units: Perinatal Research Branch

Man Years:

Total:	0.0
Professional:	0.0
Other:	0.0

Project Description:

The study has been completed and was presented at the Second Scientific Meeting of the Collaborative Study on Cerebral Palsy, Mental Retardation and other Neurological and Sensory Disorders of Infancy and Childhood, March 24-25, 1966 at the Statler-Hilton Hotel, Washington, D. C.

Honors and Awards: None

Publications: None

Serial No. NDB (CF)-66 PR/OC 1357
1. Perinatal Research Branch
2. Office of the Chief
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Prior Pregnancy Loss and Present Infant Outcome

Previous Serial Number: NDB (CF)-66 PR/SA 1357

Principal Investigator: W. S. Jones, M.D.
Brown University, Providence, R.I.

Other Investigators: R.H. Holden, Brown University, Providence, R.I.

Cooperating Units: Perinatal Research Branch, NINDB

Man Years:

Total:	0.4
Professional:	0.2
Others:	0.2

Project Description:

That a poor reproductive past performance, by any woman for whatever reason, predisposes to an even smaller yield in future pregnancies is an accepted obstetrical concept. Many components interact and/or combine to correlate prior loss with fetal death in the current pregnancy. This study attempts to isolate and evaluate the factors involved.

The perinatal loss of some 25,000 women, approximately half the Collaborative Study, who produced a single fetus in the current pregnancy, is related to loss in previous pregnancies. 43.4 percent of the women were white, 47.5 percent Negro, and about 9 percent Puerto Rican. Roughly one-third were primiparous, one-third had one or two previous pregnancies, and the remaining third had three or more.

One-third of the women with at least one prior pregnancy had one or more prior fetal losses. The combined fetal and neonatal mortality rate of 6.9 percent in women with at least one prior loss is more than twice the rate of 3.2 percent for those without prior loss.

The combined abortion, stillbirth, and neonatal death rates in the current pregnancy show a significant association with the incidence of past failures. Peak mortality rates are concentrated in regions of heavy losses in prior pregnancies. Furthermore, the greatest relative frequency of each type of

death in the study occurs for the same type of death in the last prior pregnancy.

Frequency of prior loss closely associates with shortened gestation and attendant low birth weight, which obviously escalates neonatal mortality. Low Apgar scores, respiratory distress, neonatal infections, and early neurological abnormalities all show a trend of increased hazard in rough proportion to previous infant loss, with the findings consistent by race.

Both "high risk" age groups, teenagers and women 35 and older, demonstrate a deteriorating fetal salvage closely parallel to prior pregnancy loss.

Medical and obstetrical complications are a veritable jungle. Maternal factors include small stature, uterine abnormalities, leiomyomata, and incompetent cervix. Diabetes, syphilis, toxemia, and psychosis are significant medical conditions. Obstetrical variants comprise hydramios, premature rupture of membranes, prolonged labor, dystocia, breech presentation, abruptio, placenta previa, and ceserean section. Since seldom less than two and often five or more of these factors influence most complicated cases, the computers provide less meaningful information in any specific area; nevertheless, there is definite orientation of the poorest results in the current study to the greatest perinatal loss in prior pregnancies.

Summarizing: Analysis of 25,000 women indicates that gestational background has prognostic value of statistical significance. Probability of a successful outcome in the current pregnancy, among women with prior reproductive failures, diminishes in very close relationship to the number of previous losses.

Paper read at Second Scientific Meeting of the Collaborative Study, March 24-25, 1966, Washington, D.C.

Honors and Awards: None

Publications: None

Serial No. NDB (CF)-66 PR/OC 1358
1. Perinatal Research Branch
2. Office of the Chief
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Dilatation Curves

Previous Serial Number: NDB (CF)-66 PR/SA 1358

Principal Investigator: Kenneth R. Niswander, M.D.,
University of Buffalo, Buffalo, N.Y.

Other Investigators: E. Friedman, M.D.
Michael Reese Hospital, Chicago, Illinois

Cooperating Units: Perinatal Research Branch, NINDB

Man Years:

Total:	0.6
Professional:	0.5
Other:	0.1

Project Description:

This study, whereas currently in progress, entails the production of dilatation curves from the case records of some 1,000 women whose labors were complicated either by maternal dystocia, fetal dystocia, or uterine dysfunction.

Study is in progress.

Honors and Awards: None

Publications: None

Serial No. NDB (CF)-66 PR/OC 1359
1. Perinatal Research Branch
2. Office of the Chief
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Neonatal Pneumonia in Liveborn Infants

Previous Serial Number: Serial No. NDB (CF)-66 PR/SA 1359

Principal Investigator: Sheldon B. Korones, M.D.
University of Tennessee Medical College,
Memphis, Tennessee

Other Investigators: H. Abramson, M.D., New York Medical College,
New York, N. Y.
T. Fujikura, M.D., PRB, NINDB
A. Kantor, Office of Biometry, NINDB

Cooperating Units: Perinatal Research Branch, NINDB

Man Years:

Total:	0.7
Professional:	0.6
Other:	0.1

Project Description:

Pneumonia has been cited frequently as the significant cause of neonatal mortality. The Collaborative Study's experience with neonatal pneumonia in liveborn infants was therefore analyzed in regard to significant obstetric factors and selected aspects of the clinical course of affected infants.

Records of 42,205 liveborn infants were screened for the diagnosis of pneumonia during the nursery course. Individual consideration of 191 records with this diagnosis yielded charts of 95 infants for whom the clinical impression of pneumonia was supported by radiologic evidence, by microscopic evidence at necropsy, or both. Infants were excluded from the Study group when, in addition to pneumonia, they were noted to have major congenital anomalies, multiple sites of infection with or without septicemia, or antecedent surgical procedures. Available data precluded consideration of etiologic agents.

Incidence of pertinent obstetric factors associated with birth of infants with pneumonia was compared to that of the Collaborative Study as a whole. Sixteen percent of the infants with pneumonia were delivered by Ceserean section and 6.4% by breech extraction. Maternal complications and evidence of intrauterine fetal distress were common findings. Though 46% of the infants weighed more

than 2500 grams at birth, a distinct association between low birth weight and incidence of pneumonia was noted. Prolonged interval between rupture of membranes and delivery was considerably increased in frequency among infants with pneumonia. Most infants manifested respiratory difficulty in the first 20 minutes of life. Fatality in the group studied was 46.3%.

Manuscript has been prepared and is being submitted for publication merit review.

Honors and Awards: None

Publications: None

Serial No. NDB (CF)-66 PR/OC 1360
1. Perinatal Research Branch
2. Office of the Chief
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Neonatal Serum Bilirubin Levels and Subsequent Neurologic Deficits

Previous Serial Number: NDB (CF)-66 PR/SA 1360

Principal Investigator: Thomas R. Boggs, M.D.,
Children's Hospital, Philadelphia, Pa.

Other Investigators: J. Hardy, M.D., Johns Hopkins University,
Baltimore, Maryland
T.M. Frazier, District of Columbia Health Department,
Washington, D.C.

Cooperating Units: Perinatal Research Branch, NINDB

Man Years:

Total:	0.6
Professional:	0.4
Other:	0.2

Project Description:

This study has been reported under Serial No. NDB (CF)-63 PR/PN 1156.

Honors and Awards: None

Publications: Boggs, T.R., Jr., Hardy, J.B. & Frazier, T.M.: Correlation of Neonatal Serum Total Bilirubin Concentrations and Developmental Status at Age Eight Months. J. Pediat. 71:4, 553-560, Oct. 1967

Serial No. NDB (CF)-66 PR/OC 1361
1. Perinatal Research Branch
2. Office of the Chief
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Marginal Sinus Rupture

Previous Serial Number: NDB (CF)-66 PR/SA 1361

Principal Investigator: Kenneth R. Niswander, M.D.
University of Buffalo, Buffalo, New York

Other Investigators: Milton Westphal, M.D.
University of Buffalo, Buffalo, New York

Cooperating Units: Perinatal Research Branch, NINDB

Man Years:

Total:	0.3
Professional:	0.2
Other:	0.1

Project Description:

Objectives: To determine the effects of marginal sinus rupture on the fetus, and the characteristics of the pregnant woman that predisposes her to the complication.

Methods: An abstract sheet, covering all variables chosen for study has been filled out for the Collaborative Project cases on which the definitive diagnosis of marginal sinus rupture can be made. Original listings were drawn from a screening form, OB-60, on which tentative diagnoses are made. The control group for the marginal sinus rupture group is the total study population.

Study has been completed.

Honors and Awards: None

Publications: Niswander, K.R., Berendes, H.W., Deutschberger, J., Weiss, W., Lipko, N. & Kantor, A.G.: Fetal morbidity following potentially anoxigenic obstetric conditions. VI. Rupture of the marginal sinus. Amer. J. of Obstet. Gynec. 100:6, 862-866, Mar. 1968

Serial No. NDB (CF)-66 PR/OC 1363
1. Perinatal Research Branch
2. Office of the Chief
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Early Signs of Neurologic Disorders

Previous Serial Number: Serial No. NDB (CF)-66 PR/SA 1363

Principal Investigator: Marguerite J. Gates, M.D.
Columbia University, New York, New York

Other Investigators: Pediatric Staff, Babies Hospital, New York, New York

Cooperating Units: Perinatal Research Branch, NINDB

Man Years:

Total:	-
Professional:	-
Other:	-

Project Description:

To attempt to determine if neurologic disorders of infancy and childhood can be predicted on the basis of early observation. Cases for this study are those observed in Babies Hospital, New York, New York. Several hundreds of variables are under study.

This study is still in progress.

Honors and Awards: None

Publications: None

Serial No. NDB (CF)-66 PR/OC 1366
1. Perinatal Research Branch
2. Office of the Chief
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: The Incompetent Cervix

Previous Serial Number: NDB (CF)-66 PR/SA 1366

Principal Investigator: Luke Gillespie, M.D.,
Boston Lying-In Hospital, Boston, Mass.
Heinz Berendes, M.D., PRB, NINDB

Other Investigators: J. Deutschberger, Office of Biometry, NINDB
N. Lloyd, PRB, NINDB

Cooperating Units: Perinatal Research Branch, NINDB

Man Years:

Total:	0.9
Professional:	0.8
Other:	0.1

Project Description:

The surgical treatment of the incompetent cervical os is a relatively recent development in the practice of obstetrics. The diagnosis of the syndrome is not easily made, and more often than not is probably presumptive; indeed, there are obstetricians who doubt the existence of this entity.

Data, however, have been accumulating in the literature indicating the beneficial effects of operations (of one type or another) when the diagnosis is made. This report is intended to add to the detail by presenting observations drawn from the large-scale Collaborative Project.

A thorough review of some 25,000 antenatal histories produced 72 women for whom a verified diagnosis of incompetent cervix was made during the course of their first pregnancy in the Collaborative Project. Of these women, 26 never had operations, 6 were treated surgically only in some prior pregnancy, and 40 were subjected to operations during the course of the pregnancy under study.

The 72 women involved, who averaged some five pregnancies prior to that studied, had a history notable for loss, with about 70% of their pregnancies terminating in failure.

In the pregnancies studied here, the women who had no operations continued to have a high rate of loss, despite the special care they obtained from Project physicians. Moreover, the children of these pregnancies who survived the neonatal period gave strong evidence of neurological damage.

The loss rate among women on whom operations were performed during the study was 22%. This is high by any standard, but, in the light of their past histories, represents a substantial gain. In addition, damage to survivors did not appear to be extensive.

There are no overt differences in the gravidas that would lead to the conclusion that the effects noted derive from factors other than treatment. The groups do not appear to be overly different in terms of age, gravidity, work history, gynecological background, etc.

No distinction is made here among types of surgical procedures. While a variety of methods were used, there was no maternal mortality or alarming morbidity associated with any.

The suggestion is offered that surgical correction of the cervix may be a non-specific treatment for women with a history of chronic pregnancy loss, and that a therapeutic trial might be undertaken without breach of ethical considerations.

This study has been revised and a final manuscript is being prepared for submission for publication merit review.

Honors and Awards: None

Publications: None

Serial No. NDB (CF)-66 PR/OC 1367
1. Perinatal Research Branch
2. Office of the Chief
3. Bethesda, Maryland

PHS-NIH
Individual Project Reports
July 1, 1967 through June 30, 1968

Project Title: The Relationship of Certain Demographic Variables to the Conditions and Complications of Pregnancy.

Previous Serial Number: NDB (CF)-66 PR/SA 1367

Principal Investigator: Sam P. Patterson, M.D.,
University of Tennessee Medical College,
Memphis, Tennessee

Other Investigators: S. B. Korones, M.D., University of Tennessee
J. Deutschberger, Office of Biometry, NINDB
W. Weiss, Office of Biometry, NINDB

Cooperating Units: Perinatal Research Branch, NINDB

Man Years:

Total:	0.5
Professional:	0.4
Other:	0.1

Project Description:

The measurement of a relationship between an event or condition of pregnancy and pregnancy outcome is always made complex by the intrusion of associated factors, as for example, the variable parity complicates the assessment of the relationship between duration of labor and the size of the fetus.

This communication reports the measurement of the relationships among certain demographic variables and some 35 selected conditions and complications of pregnancy. Its purpose is to offer a base for determining which of these variables should be taken into account in studies of the effects of the conditions on the outcomes of pregnancy.

The variables under study are race of gravida, age, parity, and the measures of socio-economic state, family income and housing density. In addition, individual tabulations are derived for each of 6 of the hospitals of the Collaborative Project, in which the patient population is not mainly comprised of single racial group.

Many conditions and complications of pregnancy--as, for example, toxemia, anemia, leiomyomas, KUB infections, viral infections, uterine dysfunction

and maternal dystocia—appear to bear strong relationships to one or more of the study variables. The detailing of these relationships provides a preliminary for the study in depth within the Collaborative Project of the effects of the conditions on the outcomes of pregnancy.

This study has been completed and shall be incorporated, after revision, into the Basic Document.

Honors and Awards: None

Publications: None

Serial No. NDB (CF)-66 PR/OC 1369
1. Perinatal Research Branch
2. Office of the Chief
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Spontaneous Premature Rupture of the Membrane

Previous Serial Number: None

Principal Investigator: R. S. Sappenfield, M.D.,
Charity Hospital, New Orleans, La.

Other Investigators: J. P. Mule, Charity Hospital, New Orleans, La.
H. Berendes, M.D., PRB, NINDB
W. Weiss, Office of Biometry, NINDB

Cooperating Units: Perinatal Research Branch, NINDB

Man Years:

Total:	.05
Professional:	.04
Other:	.01

Project Description:

Review of the data from the literature and from Charity Hospital in New Orleans suggested that an increased rate of perinatal morbidity and mortality is associated with the occurrence of spontaneous premature rupture of the membrane during pregnancy. This study describes an attempt to confirm and better define this association and to delineate factors related to increased incidence of premature rupture.

The operational definitions chosen for this study included those patients with premature rupture of the membrane before or after one hour preceding the onset of labor. This definition was chosen in relation to difficulties of establishing the onset of rupture and the onset of labor. Patients with induced labor followed by spontaneous or artificial rupture of the membrane and artificial rupture followed by spontaneous or induced labor were removed from further consideration because the interference made it impossible to define their status as to the natural occurrence of spontaneous premature rupture. Other limitations of this study will be presented.

In order to consider birthweight and gestation time when considering the association of spontaneous rupture (premature) to pregnancy outcome, a formula of:

$$\frac{\text{No. with premature rupture}}{\text{No. delivered}}$$

within the various gestational or birth weight groups was used. This formula allows the influence of other possible causes of premature labor or low birth weight to be demonstrated along with the influence of premature rupture.

When the associations with the increased occurrence of premature rupture were studied, a formula of:

$$\frac{\text{No. with premature rupture occurring during a given gestational period}}{\text{Total number of pregnancies exposed to that period of gestation}}$$

was used.

This last rate is believed to be a better estimate of the incidence of premature rupture and removes the effects of other possible causes of premature labor.

In view of the data received thus far from the Collaborative Study, this allows us to describe the following relationships:

a. The relative degree of association of spontaneous premature rupture of the membrane to low birth weight and short gestation, thus indicating the relationship to "high risk" infants.

b. The association of spontaneous premature rupture with congenital anomalies or abnormal presentation in the infant.

c. The consistency of the above associations among the different population groups by race, maternal age, parity and other maternal complications.

d. An estimate of the possible advantage if premature rupture could be prevented and if prevention of premature rupture could prevent premature labor.

e. The relationship of rate of occurrence of spontaneous premature rupture to gestational interval.

f. The effect of race, parity, maternal age and other maternal complications or factors associated with these variables on the rate of occurrence of spontaneous premature rupture at various gestational intervals.

g. To indicate field in which study of the etiology of premature rupture is likely to be effective.

Study is still in progress.

Honors and Awards: None

Publications: None

Serial No. NDB (CF)-66 PR/OC 1371
1. Perinatal Research Branch
2. Office of the Chief
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: The Epidemiology of Neonatal Seizures

Previous Serial Number: None

Principal Investigator: W.W. Clark, Jr., M.D.,
University of Oregon, Portland, Oregon

Other Investigators: H. Berendes, M.D., PRB, NINDB
A. Kantor, Office of Biometry, NINDB
J.S. Nemore, PRB, NINDB

Cooperating Units: None

Man Years:

Total:	0.5
Professional:	0.3
Other:	0.2

Project Description:

The Collaborative Study has thus far identified 96 infants with documented seizures in the neonatal period. Approximately 40% of these were of unknown origin. Of the 55 cases with known origin, approximately half are associated with birth insult, 30% with infection, and 10% each with developmental CNS malformation or metabolic disease.

The prognosis of these infants is bleak. In excess of 30 percent are premature by gestation, and though males are strongly predominant, a similar prematurity rate is found when birthweight is the criterion. Almost 30 percent do not survive the neonatal period; another 8.5 percent die before one year, and another 4 percent are dead by age 5. Some 7 percent of the infants have maximum serum bilirubins of at least 20 mg percent, and more than 1/3 have one-minute Apgar scores of 0 to 3.

Morbidity persists in the survivors at later examinations. At eight-months, their rate of low mental and motor scores is more than twice that of the Study population; at one-year the rate of neurologic abnormalities is 9 times the normal rate.

The characteristics and conditions of pregnancy of the gravidas of infants with convulsions imply increased risk of pregnancy outcome. While the proportions of Negroes and whites are similar to those of the Study population, mothers of

infants with convulsions are significantly older and of higher parity. They have a several-fold increase in extended labors, in their rates of placenta previa, abruptio placentae, and prolapsed cord. Four times as many of these women are cesarean sectioned, or delivered by breech, as would be expected.

Within the limitations of the number of cases available for study, the variables described above are examined by etiological source of the convulsions.

Manuscript is being submitted for publication on an amplification of the above data.

Honors and Awards: None

Publications: None

Serial No. NDB (CF)-66 PR/OC 1373
1. Perinatal Research Branch
2. Office of the Chief
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: The Effects of the Duration of Labor on the Fetus

Previous Serial Number: None

Principal Investigator: Kenneth R. Niswander, M.D.
University of Buffalo, Buffalo, New York

Other Investigators: Zekin A. Shakhashiri, M.D., PRB, NINDB

Cooperating Units: Perinatal Research Branch, NINDB

Man Years:

Total:	0.4
Professional:	0.3
Other:	0.1

Project Description:

Objectives: To determine the effect on the fetus of the duration of labor.

Methods: Prior work has identified certain complications of pregnancy (such as abruptio placentae, fetal and maternal dystocia, uterine dysfunction) that are not randomly distributed over the course of labor; these may account for the untoward effects found in conjunction with very short or very long labors. As a consequence, by holding these complications constant, it is likely that the effects of duration of labor per se can be measured.

Outcomes used were: Mortality, Apgar Scores at one and five minutes, and findings throughout the first year of life, both on neurological and psychological examinations. Birthweight and parity were used as controls (race has been shown in a prior study not to be related to duration of labor, and is therefore not an essential control).

Results: With certain complications equated out, there is no apparent untoward effect of duration. That is, if, apparently, there is no dysfunction or dystocia, the labor of long duration is relatively uncomplicated and does not produce immediate or long-lasting (throughout the first year of life) difficulties for the fetus.

Study has been temporarily shelved.

Honors and Awards: None

Publications: None

Serial No. NDB (CF)-66 PR/OC 1374
1. Perinatal Research Branch
2. Office of the Chief
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Complications of Pregnancy in Relation to the Duration of Labor

Previous Serial Number: None

Principal Investigator: Kenneth R. Niswander, M.D.,
University of Buffalo, Buffalo, New York

Other Investigators: M. Westphal, M.D., University of Buffalo
H. Berendes, M.D., PRB, NINDB
J. Deutschberger, Office of Biometry, NINDB
W. Weiss, Office of Biometry, NINDB

Cooperating Units: Perinatal Research Branch, NINDB

Man Years:

Total:	0.6
Professional:	0.4
Other:	0.2

Project Description:

Objectives: Obstetricians have long accepted that either prolonged or fairly precipitous labor increases the hazard of perinatal death. The question as to whether the length of labor per se is responsible for the added hazard, or whether in fact certain complications of pregnancy are associated with the duration of labor, and the hazard is an effect of the complication.

This research then is designed to determine whether certain complications of pregnancy are randomly distributed over all durations of labor, or are closely associated with particular intervals.

Methods Employed: Some 25 conditions and complications of pregnancy were measured against duration of labor, with factors such as parity and race held constant.

Major Findings: Abruptio placentae is related to short labor, while uterine dysfunction, maternal dystocia, and fetal dystocia are closely correlated with excessively long labor. The length of labor does not appear to be associated with conditions or complications such as placenta previa, prolapsed cord, marginal sinus rupture, or the presence in the gravia of toxemia, organic heart

disease, asthma, bacteriuria, etc.

In a proper study, then, of the effects of duration of labor, those complications associated with particular intervals should be held constant, so as to avoid the possible bias of the effect of the complication.

Study has been temporarily shelved.

Honors and Awards: None

Publications: None

Serial No. NDB (CF)-66 PR/OC 1376
1. Perinatal Research Branch
2. Office of the Chief
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Organic Heart Disease in Pregnancy

Previous Serial Number: None

Principal Investigator: Kenneth R. Niswander, M.D.
Children's Hospital of Buffalo, Buffalo, New York

Other Investigators: H. Berendes, M.D., PRB,NINDB
J. Deutschberger, Office of Biometry, NINDB
M. Westphal, M.D., Children's Hospital of Buffalo, Buffalo, New York
N. Lipko, PRB, NINDB

Cooperating Units: Perinatal Research Branch, NINDB

Man Years:

Total:	0.5
Professional:	0.4
Other:	0.1

Project Description:

Reports in the literature have stipulated the risk of perinatal mortality in cases in which the pregnant woman is suffering heart disease. The consensus is that the risk is substantial even in asymptomatic cardiac patients and increases readily with the severity of the disease.

In the investigation reported here, 327 pregnancies in which organic heart disease was authenticated were studied. Assessments were made of the outcomes of these pregnancies, both immediate and through the first year of life of the surviving infant.

The perinatal loss rate in these 327 cases was relatively high, but not as great as that found by earlier investigators. The severity of the disease as judged by limitation of activity and by digitalis therapy appears to be a factor in outcome; as other investigators have noted, however, proper prenatal care apparently produces a beneficial and salvaging effect on pregnancies complicated by heart disease.

While severe heart disease is associated with the production of low birthweight children and of children who exhibit an increase in morbidity during the neonatal period, as evidenced by low Apgar scores, the long-term

prognosis for children who survive the perinatal period does not appear to be overly poor. The one-year status of children of mothers with heart disease suggests that serious neurological problems are indeed quite rare. Severe maternal organic heart disease certainly might lead to anoxic episodes in the fetus. The lack of a clear-cut demonstration of an effect on the central nervous system of surviving children as shown by these data thus far could be due to the limitations of a one-year neurological examination in identifying more subtle neurological deficits and/or effects on higher intellectual and perceptual functions which cannot be identified in young infants.

More work continues on this study. First phase already published.

Honors and Awards: None

Publications: Niswander, K., Berendes, H., Deutschberger, J., Lipko, N. and Westphal, M.C.: Fetal morbidity following potentially anoxigenic obstetric conditions. V. Organic heart disease. Amer. J. Obstet. Gynec. 98:6, 871-876, Jul. 1967.

Serial No. NDB (CF)-66 PR/OC 1377
1. Perinatal Research Branch
2. Office of the Chief
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Reproductive Wastage in Bronchial Asthma

Previous Serial Number: None

Principal Investigator: Myron Gordon, M.D.
New York Medical College, New York, N.Y.

Other Investigators: K. R. Niswander, M.D., Univ. of Buffalo, N.Y.
H. Berendes, M.D., PRB, NINDB
A. Kantor, Office of Biometry, NINDB
N. Lloyd, PRB, NINDB

Cooperating Units: Perinatal Research Branch, NINDB

Man Years:

Total:	0.0
Professional:	0.0
Other:	0.0

Project Description:

Manuscript is being submitted for publication merit review.

Honors and Awards: None

Publications: None

Serial No. NDB (CF)-66 PR/OC 1378
1. Perinatal Research Branch
2. Office of the Chief
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: The Prediction of Birth Weight-Multivariate Analysis

Previous Serial Number: None

Principal Investigator: Heinz W. Berendes, M.D., PRB, NINDB

Other Investigators: W. Weiss, Office of Biometry, NINDB
J. Deutschberger, Office of Biometry, NINDB
Z. Shakhashiri, M.D., PRB, NINDB
E. Jackson, Office of Biometry, NINDB

Cooperating Units: Perinatal Research Branch, NINDB

Man Years:

Total:	0.7
Professional:	0.5
Other:	0.2

Project Description:

In the Collaborative Project, the birth weight of the infant is the best predictor, by far, of neonatal mortality and of almost every characteristic of morbidity in the study.

Birth weight, then, merits intensive investigation. It is fortunate that this variable has attributes conducive to statistical treatment; it is always reported, it is measured with considerable precision and it is continuous over a wide range of values.

This communication reports on two aspects of a study of birth weight. The first is directed towards the identification of those characteristics and conditions of pregnancy which will, most precisely, estimate the birth weight of the infant. The variables studied range in time, relative to the period of pregnancy, from those available prior to the study pregnancy, to those which are measured in the stages of labor and delivery.

The identification of those variables, which, taken together, provide the means for estimating birth weight within narrow limits, may lead to increased understanding of the role of these variables in their association with birth weight.

The practical aspect of prediction-that is, the measure of the availability and contribution of important characteristics for predicting birth weight, by time sequence, during the period of pregnancy, is discussed.

On the basis of the prior examination of study data, a total of 38 variables were selected for a multiple regression study of birth weight.

The birth weights of the children of some 6600 whites and 8000 Negroes, who had at least one prior pregnancy, were evaluated separately by race.

Of the 38 considered, 21 variables and 30 variables, for whites and Negroes respectively, show significant association with birth weight. Despite the larger number of significant variables, the correlation with birth weight is less for Negroes than for whites.

Study has been amplified and is being further analyzed in preparation for the manuscript.

Honors and Awards: None

Publications: None

Serial No. NDB (CF)-66 PR/OC 1379
1. Perinatal Research Branch
2. Office of the Chief
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Fetal Heart Rate in Relation to Pregnancy Outcome

Previous Serial Number: None

Principal Investigators: Ralph C. Benson, M.D.,
Univ. of Oregon Medical School
Portland, Oregon
H. Berendes, M.D., PRB, NINDB

Other Investigators: F. Shubeck, M.D., Univ. of Oregon Medical School
W. Weiss, Office of Biometry, PRB, NINDB
J. Deutschberger, Office of Biometry, PRB, NINDB
Z. Shakhashiri, M.D., PRB, NINDB

Cooperating Units: None

Man Years:

Total:	0.7
Professional:	0.5
Other:	0.2

Project Description:

Objectives: To identify a fetal heart rate factor which would be a sensitive indicator of fetal distress.

Methods Employed: Fine Fetal heart rate factors, which include the lowest rates, the variability in rates, sudden drops in rate, and consecutive drops in rate were compared against indices of fetal mortality and fetal morbidity, as well as morbidity up to one year of age, with such factors as the birthweight, use of anesthesia, stage of labor and number of heart rate observations kept constant.

Major Findings: The fine fetal heart rate variables form a hierarchy in their degree of sensitivity as predictors of fetal distress. The significant associations of these variables appear to be exclusively with stillbirths and neonatal death rates, and with the five-minute Apgar score. Little association is noted with the other indices of morbidity studied.

Manuscript has been submitted for publication in a textbook and in addition, additional data are being analyzed for a subsequent publication.

Honors and Awards: None

Publications: None

Serial No. NDB (CF)-66 PR/OC 1382
1. Perinatal Research Branch
2. Office of the Chief
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: The Effects of Maternal Diabetes

Previous Serial Number: None

Principal Investigator: Luke Gillespie, M.D.,
Boston Lying-In Hospital, Boston, Mass.

Other Investigators: A. Grimaldi, M.D.,
New York Medical College, New York
Zekin A. Shakhashiri, M.D., PRB, NINDB

Cooperating Units: Perinatal Research Branch, NINDB

Man Years: (estimated)

Total:	1.4
Professional:	1.1
Other:	0.3

Project Description:

This study has been revised and incorporated into Study reported under Serial No. NDB (CF)-68 PR/PN 1635.

Honors and Awards: None

Publications: None

Serial No. NDB (CF)-66 PR/OC 1383
1. Perinatal Research Branch
2. Office of the Chief
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Certain Socio-cultural Parameters in Relation to Pregnancy Outcome

Previous Serial Number: None

Principal Investigator: Zekin A. Shakhashiri, M.D., PRB, NINDB

Other Investigatros: H. Berendes, M.D., PRB, NINDB
W. Weiss, Office of Biometry, NINDB
J. Deutschberger, Office of Biometry, NINDB

Cooperating Units: Perinatal Research Branch, NINDB

Man Years:

Total:	0.4
Professional:	0.3
Other:	0.1

Project Description:

It is generally assumed that socio-cultural status is an indicator of pregnancy outcome, although there are few hard findings to bear out this suggestion. Moreover, data developed in this area almost invariably refer to the gravida, more than to the father of the child.

For this study, so-called socio-cultural variables are measured for both gravida and father of child, and are taken in combination with respect to outcome.

Other measurements, such as age of gravida and of father of child, are taken in combination in similar fashion and related to outcome. While these variables do not qualify as purely of a socio-cultural nature, they do fit in with the general study plan, and it is economical of effort to deal with them in the course of this study.

Study, as such, has been deleted and its concept has been incorporated in the effort to prepare the Basic Document of the Study.

Honors and Awards: None

Publications: None

Serial No. NDB (CF)-68 PR/OC 1618
1. Perinatal Research Branch
2. Office of the Chief
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: The Effect of Labor on the Outcome of the Child

Previous Serial Number: None

Principal Investigators: Z. A. Shakhashiri, M.D., PRB, NINDB
W. Lawrence Holley, M.D., PRB, NINDB
A. A. Lilien, M.D., PRB, NINDB

Other Investigators: None

Cooperating Units: Perinatal Research Branch, NINDB

Man Years:

Total:	.08
Professional:	.06
Other:	.02

Project Description:

In order to single out the effect of labor, if any, on fetal growth and development, a study is made of outcomes of normal pregnancies terminated spontaneously, compared to outcomes of similar pregnancies terminated by elective induction of labor and to outcomes of similar pregnancies terminated by elective cesarean section.

Methods Employed: Project infants of normal pregnancies terminated as described above will be compared for selected outcome variables such as mortality, Apgar, bilirubin, mental and motor scores at eight months and I.Q. at four years. All three groups will be controlled for race, birth weight and gestation length.

Major Findings: A search is under way to ascertain whether cases are available in adequate numbers to make the design feasible. Additional non-Project cases might be needed.

The Study is in progress.

Honors and Awards: None

Publications: None

Serial No. NDB (CF)-66 PR/OB 1327
1. Perinatal Research Branch
2. Section on Obstetrics
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Maternal Deaths in the Collaborative Project

Previous Serial Number: Same

Principal Investigator: Jose G. Marmol, M.D., PRB, NINDB

Other Investigators: Rudolf F. Vollman, M.D., PRB, NINDB
Myron Gordon, M.D., New York Medical College
Sam P. Patterson, M.D., University of Tennessee
William A. Reid, M.D., Providence Lying-In Hospital

Cooperating Units: All institutions participating in the Collaborative Study

Man Years

Total:	0.5
Professional:	0.3
Other:	0.2

Project Description:

Major Findings: For a total of 37,545 live births registered in the Collaborative Project since its beginning in 1959 through June 1965, 40 maternal deaths were reported. In all of the cases a definite diagnosis of the cause of death was established. Sixteen of the 40 deaths were attributed to direct obstetric causes, all of these were Negroes. Among the direct obstetric causes of death, infections (6 cases) occupy the first place, followed by vascular accidents (4 cases), anesthesia complications (3 cases), hemorrhage (2 cases), and toxemia (1 case). No deaths related to placenta previa or abruptio placentae were reported in the study, nor were there any deaths due to ectopic pregnancy.

In the category of indirect obstetric causes of death (14 cases), four mothers died from cardiac diseases, three from pulmonary conditions, two from vascular diseases, two from lupus erythematosus, and one each from hepatic, metabolic, and sickle cell disease. Of the maternal deaths not related to pregnancy, five were due to accidents.

A minute review of each case of maternal death as to its preventability revealed clearly that a ceiling of therapeutic effectiveness in the reduction of maternal deaths is approaching. Therefore, the hypothesis was tested if

in the future maternal mortality could be reduced by identifying non-pregnant women who are potentially high-risk mothers in whom pregnancy would be a life-endangering complication. Using the criteria for high-risk mothers established by the Maternity and Infant Care Project of the New York City Department of Health, 28 of the 40 maternal deaths were classified as high-risk mothers prior to conception. It is felt that in this group of high-risk women a major reduction in maternal mortality can be achieved through adequate family planning.

Honors and Awards: None

Publications: Marmol, J.G., Vollman, R.F., Gordon, M., Patterson, S.P., and Reid, W.A.: Maternal death and high-risk pregnancy: an analysis of 40 maternal deaths in the Collaborative Project. Obstet. Gynec. 30: 816-820, Dec. 1967.

Serial No. NDB (CF)-66 PR/OB 1328
1. Perinatal Research Branch
2. Section on Obstetrics
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Evaluation of the Possible Teratogenic Effect of Antihistaminic Drugs Taken During Pregnancy

Previous Serial Number: Same

Principal Investigator: Rudolf F. Vollman, M.D., PRB, NINDB

Other Investigators: Jose G. Marmol, M.D., PRB, NINDB
Irene B. Ross, PRB, NINDB
Alan L. Scriggins, M.D., PRB, NINDB
James H. Tarver, Jr., PRB, NINDB

Cooperating Units: None

Man Years

Total:	0.3
Professional:	0.2
Other:	0.1

Project Description:

Major Findings: The types and frequency of congenital malformations in the offspring of mothers who reported an intake of any one of five specified antihistaminic drugs during pregnancy have been analyzed. Of 34,240 mothers whose pregnancies terminated in single births between 1959 and 1964 in the Collaborative Project, five sub-samples were selected, each one composed of all gravidae who reported an intake of one of the specified drugs. All other drugs reported in addition to the five antihistaminics were not considered. No significant differences in the types and frequency of malformations by drug groups could be established when controlled for age, race, gravidity, parity, marital status, malformations reported in siblings, and weeks of gestation in which the drug was first taken.

Paper read at the annual meeting of the American Association of Anatomists, Kansas City, Missouri, April 4-7, 1967, and published as an abstract in Anat. Rec. 157: 337, Feb. 1967.

Honors and Awards: None

Publications: None

Serial No. NDB (CF)-66 PR/OB 1330
1. Perinatal Research Branch
2. Section on Obstetrics
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: The Length of the Premenstrual Phase by Age of Women

Previous Serial Number: Same

Principal Investigator: Rudolf F. Vollman, M.D., PRB, NINDB

Other Investigators: None

Cooperating Units: None

Man Years

Total:	0.1
Professional:	0.1
Other:	0.0

Project Description:

Major Findings: Monophasic temperature curves have been observed most frequently immediately after menarche (45 percent of all cycles) with a consistently decreasing rate during adolescent development. Between 23 and 44 years of age, an average of only 2 percent of the BBT curves are monophasic. At age 45 the rate of the anovulatory cycles steadily increases toward menopause.

BBT curves with short premenstrual phases of from three to 10 days' duration have been found in 44 percent of all cycles after menarche. The rate decreases in the course of adolescence to about 15 percent during the phase of maturity, with little change during the premenopause.

Premenstrual phases of 11 to 16 days' duration are infrequent immediately after menarche, but comprise about 80 percent of all cycles between ages 23 and 44 years, with decreasing rates during the premenopause.

These age changes in the ovulatory cycle do not seem to be directly correlated with female fertility; high conception rates during the adolescent phase contradict the low ovulatory rates during the same period.

Paper presented at the Fifth World Congress on Fertility and Sterility, Stockholm, June 16-22, 1966.

Honors and Awards: None

Publications: Vollman, R.F.: The length of the premenstrual phase by age of women. In Proceedings of the Fifth World Congress on Fertility and Sterility, Stockholm, June 16-22, 1966. Excerpta Medica Int. Cong. Ser. No. 133, pp. 1171-1175.

Serial No. NDB (CF)-66 PR/OB 1331
1. Perinatal Research Branch
2. Section on Obstetrics
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Obstetric Factors in Twin Pregnancies

Previous Serial Number: Same

Principal Investigator: Rudolf F. Vollman, M.D., PRB, NINDB

Other Investigators: Jose G. Marmol, M.D., PRB, NINDB
Irene B. Ross, PRB, NINDB

Cooperating Units: All institutions participating in the Collaborative Project

Man Years

Total:	0.7
Professional:	0.5
Others:	0.2

Project Description:

Objectives: The early diagnosis of a twin pregnancy still remains an important problem on which depend the prenatal care and the management of the labor and delivery. The study has two objectives:

1. To study the outcome of twin pregnancies in relation to the time the diagnosis was first established.

2. To make a comparison of the obstetric problems presented by the first versus the second twin and their effect on the fetal outcome.

Methods: With the help of a computer printout, an established case and card file and an additional review of a current file on abortions and fetal deaths the twins delivered in the Collaborative Project through December 31, 1965, have been identified. All case records were reviewed and additional information or clarification was solicited from the collaborating hospitals as needed. The mother's medical, family and reproductive history, together with information on the course of the Study pregnancy, intercurrent diseases, drugs, obstetric complications, labor and delivery and outcome of pregnancy were abstracted. These data have been used to prepare a set of tabulations

for the study of the variables specified above. The completion of this study has been delayed due to difficulties in completing missing information. Hopefully, it will be completed during the current fiscal year.

Honors and Awards: None

Publications: None

Serial No. NDB (CF)-66 PR/OB 1332
1. Perinatal Research Branch
2. Section on Obstetrics
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Down's Syndrome and the Incidence of Infectious Hepatitis During Pregnancy

Previous Serial Number: Same

Principal Investigator: Rudolf F. Vollman, M.D., PRB, NINDB

Other Investigators: Jose G. Marmol, M.D., PRB, NINDB
Reba L. Goldman, PRB, NINDB

Cooperating Units: All institutions participating in the Collaborative Study

Man Years

Total:	0.3
Professional:	0.2
Other:	0.1

Project Description:

Major Findings: In an Australian study the epidemic occurrence of infectious hepatitis was related to an increase in the birth of mongoloid children approximately nine months after the peak of the epidemic. Perinatal Research Project data on mongoloids from Study pregnancies have been analyzed to verify or reject this hypothesis. No cases of infectious hepatitis or icterus during pregnancy were found in the Study population. This study has been completed.

Honors and Awards: None

Publications: None

Serial No. NDB (CF)-66 PR/OB 1333
1. Perinatal Research Branch
2. Section on Obstetrics
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Distribution of Abortions by Chronologic and Gynecologic Age of the Gravida

Previous Serial Number: Same

Principal Investigator: Rudolf F. Vollman, M.D., PRB, NINDB

Other Investigators: Annie W. Litz, PRB, NINDB
Jose G. Marmol, M.D., PRB, NINDB

Cooperating Units: All institutions participating in the Collaborative Study

Man Years

Total:	0.4
Professional:	0.3
Other:	0.1

Project Description:

Objectives: Information is accumulating which demonstrates that endocrine and morphologic conditions for optimal reproductive performance are reached only several years after menarche. The conventional association of pregnancy outcome by chronologic maternal age will be compared with the mother's gynecologic age, based on the age at menarche.

Methods: For Study pregnancies terminating in abortion, a number of important maternal variables will be abstracted from the Study record: race, chronologic and gynecologic age, marital status, gravidity and parity, length of the menstrual cycle, medical and obstetric complications of the Study pregnancy, duration and outcome of the Study pregnancy. These variables will serve as controls in the analysis of chronologic versus gynecologic maternal age. Due to lack of time this study has been delayed, but it will be continued.

Honors and Awards: None

Publications: None

Serial No. NDB (CF)-67 PR/OB 1507
1. Perinatal Research Branch
2. Section on Obstetrics
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: The History and Present Function of the Maternal Mortality Study Committees

Previous Title: The Decline of Maternal Mortality in the U.S.A.: A Historical Review

Previous Serial Number: Same

Principal Investigator: Jose G. Marmol, M.D., PRB, NINDB

Other Investigators: Alan L. Scriggins, M.D., PRB, NINDB

Cooperating Units: None

Man Years

Total:	0.2
Professional:	0.2
Other:	0.0

Project Description:

Objectives: To study the circumstances that led to the establishment of the Maternal Mortality Study Committees in the U.S.A., their contribution to the decline in maternal mortality rates, their present status and future plans.

Methods: A letter was sent to the Secretary of the State Medical Society of all of the States with the following request: 1) Does your State have a Maternal Mortality Study Committee? 2) When was the Committee formed and how does it operate? 3) What is the accepted definition of maternal death in your State and is it uniformly applied? Supplementary information was obtained by reviewing the journals of the States' Medical Societies. A letter was also sent to the obstetricians involved in the creation of these committees. The study is still in the process of gathering information. That available is being tabulated.

Honors and Awards: None

Publications: None

Serial No. NDB (CF)-67 PR/OB 1508
1. Perinatal Research Branch
2. Section on Obstetrics
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Sequential Pregnancy Study

Previous Serial Number: Same

Principal Investigator: Alan L. Scriggins, M.D., PRB, NINDB

Other Investigators: None

Cooperating Units: All institutions participating in the Collaborative Project

Man Years

Total:	0.4
Professional:	0.3
Other:	0.1

Project Description:

This study was completed in 1967. It was intended for use within the Branch as an indicator of some characteristics of the part of the sample with more than one pregnancy in the Study. It may also be used as an indicator of the reliability of certain obstetric data.

Major Findings: Wide differences in consistency of response were found. In general, items concerning remote history of the gravida elicited by lay interviewers were very inconsistent (except menarche), while items concerning clinical judgment by physicians were fairly consistent.

Honors and Awards: None

Publications: None

Serial No. NDB (CF)-68 PR/OB 1619
1. Perinatal Research Branch
2. Section on Obstetrics
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Obesity in Pregnancy in the Collaborative Project

Previous Serial Number: None

Principal Investigator: Arnold A. Lilien, M.D., PRB, NINDB

Other Investigators: None

Cooperating Units: None

Man Years

Total:	0.44
Professional:	0.24
Other:	0.20

Project Description:

Objectives: To resolve whether maternal obesity increases perinatal risk. Further, to identify and characterize those factors contributing to this risk.

Methods: A printout with the NINDB numbers of all gravidae in the Collaborative Project who weighed 200 lbs. or more at the time of their first clinic visit will be reviewed. The plan is to hand check the records of these gravidae for maternal, fetal and obstetrical factors as well as outcome.

Major Findings: The project is in process. The printout has been received. Abstraction of the information in the printout in conjunction with the case records is in progress.

Honors and Awards: None

Publications: None

Serial No. NDB (CF)-68 PR/OB 1620
1. Perinatal Research Branch
2. Section on Obstetrics
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Oxytocin Induced Water Intoxication

Previous Serial Number: None

Principal Investigator: Arnold A. Lilien, M.D., PRB, NINDB

Other Investigators: None

Cooperating Units: None

Man Years

Total:	0.05
Professional:	0.05
Other:	0.00

Project Description:

Objectives: To report a maternal death caused by a side reaction of a commonly used drug, oxytocin.

Methods: A case treated at the Bronx Municipal Hospital for an uncomplicated incomplete abortion in November 1966 by the author was reviewed for publication. This included a review of the pertinent literature.

Major Findings: Oxytocics administered over a period of time will cause water retention. This can seriously impair water and electrolyte balance. The first reported maternal death due to oxytocin water intoxication is described. Project is complete.

Honors and Awards: None

Publications: Lilien, A.A.: Oxytocin induced water intoxication. Accepted for publication in Obstetrics and Gynecology.

Serial No. NDB (CF)-68 PR/OB 1621
1. Perinatal Research Branch
2. Section on Obstetrics
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Term Intrapartum Fetal Demise

Previous Serial Number: None

Principal Investigator: Arnold A. Lilien, M.D., PRB, NINDB

Other Investigators: None

Cooperating Units: None

Man Years

Total:	0.70
Professional:	0.34
Other:	0.36

Project Description:

Objectives: To identify and characterize the maternal, fetal and obstetrical factors which are responsible for death of the term fetus during labor.

Methods: A hand review of all the records of term fetal and neonatal deaths up to 24 hours was done to isolate that group which died during labor. The group so defined was then reviewed for maternal, fetal and obstetrical factors which were responsible for the death. The results were compared to material available.

Major Findings: From a base population of 55,000 deliveries, 450 term fetal-neonatal deaths were reviewed and 88 term intrapartum deaths isolated. Factors responsible for the deaths were then ascertained. It was concluded that 1) there are few cases of fetal death during labor for which abnormal clinical findings cannot be found; 2) clinical studies must be used to characterize this group, not pathologic postmortem findings; and 3) prolonged rupture of membranes is prevalent in term fetal deaths during labor, although it cannot be separated from the associated pathology as the cause of the death.

Paper read at the Perinatal Research Branch research seminar on February 21, 1968. Project is now being written for publication.

Honors and Awards: None

Publications: None

Serial No. NDB (CF)-68 PR/OB 1622
1. Perinatal Research Branch
2. Section on Obstetrics
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Mothers of Mongoloids in the Collaborative Project

Previous Serial Number: None

Principal Investigator: Jose G. Marmol, M.D., PRB, NINDB

Other Investigators: Alan L. Scriggins, M.D., PRB, NINDB
Rudolf F. Vollman, M.D., PRB, NINDB

Cooperating Units: None

Man Years

Total:	0.7
Professional:	0.5
Other:	0.2

Project Description:

Objectives: To identify possible obstetric and medical (including x-rays and drugs) factors that characterize mothers of mongoloids in comparison to a matched control group.

Methods: Comparison and evaluation of incidences of medical and obstetric complications in mothers of mongoloids with a matched control group.

Major Findings: The incidence of mongolism is nearly equal in whites and Negroes. The distribution of maternal ages is bimodal, but there are more white mothers in the younger age groups and more Negroes in the older age groups. No differences were found in parity, pregnancy-free interval, number of prior abortions or events of past medical history between Study and control groups.

Birthweight and duration of pregnancy are slightly less for the Study group than for the controls. There were more male than female mongoloid infants. A very similar drug and x-ray experience in the Study and in the control group has been noted. Paper to be submitted for publication in the American Journal of Obstetrics and Gynecology.

Honors and Awards: None

Publications: None

Serial No. NDB (CF)-68 PR/OB 1623
1. Perinatal Research Branch
2. Section on Obstetrics
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Prenatal Drugs

Previous Serial Number: None

Principal Investigator: Alan L. Scriggins, M.D., PRB, NINDB

Other Investigators: Rudolf F. Vollman, M.D., PRB, NINDB
Seymour Katsh, Ph.D., National Science Foundation
S. Barbara Katz, Office of Biometry, NINDB

Cooperating Units: All institutions participating in the Collaborative Study

Man Years

Total:	1.0
Professional:	0.6
Other:	0.4

Project Description:

Objectives: To compare and contrast the reporting of different kinds of drugs in the total core population of the Collaborative Project.

Methods: A classification of all prenatal drugs coded by the Collaborative Project was devised which encompasses distinctions into unknowns and knowns and then single chemical entities and combination drugs. Knowns are then sub-divided into groups thought to be most meaningful for the clinician (e.g., single/anti-infective/antibiotic and single/anti-infective/sulfonamide etc.) by PRB personnel with clinical backgrounds. A pharmacologist acting as a consultant also reviewed the classification. A program is being devised to present the reporting of such groups of drugs by race, hospital and trimester. Another aspect of the study will be a description of the sample reporting drugs (and no drugs) by race, age and hospital. Further, the number of specific drugs reported will be related to the time of registration in the Collaborative Project for prenatal care. Utilizing the classification provided by clinicians and pharmacologist, the data will be tabulated as above by computer facilities. Study is in computer programming stage.

Honors and Awards: None

Publications: None

Serial No. NDB (CF)-68 PR/OB 1624
1. Perinatal Research Branch
2. Section on Obstetrics
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Respiratory Distress Syndrome in Babies Born to Mothers Reporting Acetazolamide During the Labor and Delivery Period

Previous Serial Number: None

Principal Investigator: Alan L. Scriggins, M.D., PRB, NINDB

Other Investigators: Arnold A. Lilien, M.D., PRB, NINDB

Cooperating Units: Charity Hospital, New Orleans, and the Medical College of Virginia

Man Years

Total:	0.2
Professional:	0.1
Other:	0.1

Project Description:

Objectives: To investigate the possible relationship between depression of the enzyme carbonic anhydrase and the respiratory distress syndrome in newborns.

Some investigators have noted depressed carbonic anhydrase in newborns with R.D.S. compared to controls. Since acetazolamide, a diuretic, acts by depression of that enzyme, it was thought that maternal ingestion of acetazolamide during labor might result in a higher rate of R.D.S. in their babies. Thus a hand review of approximately 300 cases reporting acetazolamide (divided nearly equally between two collaborating institutions) showed only two cases of R.D.S. The study has been completed and will be prepared for publication.

Honors and Awards: None

Publications: None

Serial No. NDB (CF)-68 PR/OB 1625
1. Perinatal Research Branch
2. Section on Obstetrics
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Menstruation and Ovulation in the Monkey

Previous Serial Number: None

Principal Investigator: Rudolf F. Vollman, M.D., PRB, NINDB

Other Investigators: Irene B. Ross, PRB, NINDB

Cooperating Units: Department of Embryology, Carnegie Institution of Washington

Man Years

Total:	0.5
Professional:	0.3
Other:	0.2

Project Description:

Objectives: To systematically analyze all the unpublished data collected by the late Dr. Carl G. Hartman on reproduction in the monkey.

Methods: Tabulate and analyze data on menstruation, ovulation, mating, conceptions, duration of pregnancy, birthweights, lactation and steroid hormone treatment in the monkey.

Major Findings: Work is in progress.

Honors and Awards: Memorial address to the Second International Congress of Primatology for Dr. Carl G. Hartman

Publications: None

Serial No. NDB (CF)-68 PR/OB 1626
1. Perinatal Research Branch
2. Section on Obstetrics
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Distribution of Fertile and Sterile Coitus by Days of the Menstrual Cycle

Previous Serial Number: None

Principal Investigator: Rudolf F. Vollman, M.D., PRB, NINDB

Other Investigators: None

Cooperating Units: None

Man Years

Total:	0.4
Professional:	0.3
Other:	0.1

Project Description:

Objectives: To identify the optimal time of conception in women.

Methods: Calendar records on menstruation, intercourse, basal body temperature during the menstrual cycle and pregnancy.

Major Findings: Conceptions after single intercourse by day of the menstrual cycle do not provide an estimate of the time of ovulation because of the variability in the length of the postmenstrual phase. When the point of reference is the rise of the basal body temperature, conceptions still occur within a range of 10 days and conception rates per day do not reach 20 percent, even at the optimal day. This astonishingly low rate of conceptions clearly indicates that further research in the processes of ovulation, fertilization and implantation in the human is required.

Honors and Awards: None

Publications: None

Serial No. NDB (CF)-63 PR/PN 1156
1. Perinatal Research Branch, NINDB
2. Section on Pediatric Neurology
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Neonatal Hyperbilirubinemia and Subsequent Neurological Sequelae.

Previous Serial Number: Same

Principal Investigator: Janet Hardy, M.D., Johns Hopkins Hospital

Other Investigators: T. R. Boggs, M.D., Pennsylvania Hospital
Heinz Berendes, M.D., PRB, NINDB
B. H. Williams, PRB, NINDB
William Weiss, Office of Biometry, NINDB
Joseph S. Drage, M.D., PRB, NINDB

Cooperating Units: Johns Hopkins University, Baltimore, Maryland
Pennsylvania Hospital, Philadelphia, Pennsylvania

Man Years

Total:	.05
Professional:	.05
Other:	.00

Project Description:

Approximately 23,000 infants resulting from single live births among women registered in the Collaborative Project between January 1, 1959 and June 30, 1964, have had one or more neonatal total serum bilirubin determinations performed and have been examined at 8 and 12 months of age. Correlations between the maximum observed neonatal total serum bilirubin level and subsequent neurologic deficit have been made. These correlations were made both before and after the exclusion of major congenital malformations including those of the brain, the spinal cord, the skeletal system, the kidney, the upper respiratory tract, the heart and the gastro-intestinal tract and syndromes such as mongolism, cretinism, gonadal dysgenesis, Pierre Robin's Syndrome, etc. The exclusion of such congenital malformations did not alter essentially the relationships observed before their exclusion and, therefore, infants with such defects are included in the survey. The study cases included both Coombs' positive and Coombs negative infants.

The most striking findings were those encountered on evaluating the Motor and Mental Scores (modifications of the Bayley Scale) of these infants at

their age of 8 months (± 2 weeks). There was a highly significant linear component to the regression lines of the associations between increasingly high total serum bilirubin levels and the incidence of infants performing in the lowest decile of their group as concerns motor and mental scores. Although these observations are most striking for the lower birthweight groups, they held for all birthweight groups and continued to hold after the birthweight groups were further controlled for the 5-minute Apgar score. Furthermore, the bilirubin-low mental and low motor score relationships were noted not to begin abruptly at the 20 mgm percent level but were observed to rise progressively and to become substantial at the 16 - 19 mg. percent concentration.

Honors and Awards: None

Publications: Boggs, T.R., Jr., Hardy, J.B., and Fraxier, T.M., Correlation of Neonatal Serum Total Bilirubin Concentrations and Developmental Status at Age Eight Months. J.Pediat 71:4, 553-560, Oct. 1967.

Serial No. NDB-(CF)-63 PR/PN 1162
1. Perinatal Research Branch, NINDB
2. Section on Pediatric Neurology
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title : Apgar Scores

Previous Serial Number: Same

Principal Investigator: Joseph S. Drage, M.D., PRB, NINDB

Other Investigators : None

Cooperating Units : None

Man Years

Total	:	.20
Professional:		.10
Other	:	.10

Project Description:

This study has matched one and five-minute Apgar scores of children to their performance on the four-year psychological examination. Children with certain congenital malformations have been excluded. Controls for this study are birthweight, education of gravida, race, and sex. The outcome on the four-year psychological examination is defined by the Binet I.Q. score, the Graham Block Sort Raw Scores, the assessment of fine and gross-motor development, the behavior profile, and the overall impression. Study in progress - data feedback obtained and undergoing analysis.

Honors and Awards: None

Publications : None

Serial No. NDB-(CF)-63 PR/PN 1163
1. Perinatal Research Branch, NINDB
2. Section on Pediatric Neurology
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title : An Investigation into the Relationship Between Congenital Heart and Great Vessel Anomalies and Selected Factors as Recorded in the Collaborative Perinatal Research Project

Previous Serial Number : Same

Principal Investigators: Lenore Bajda, M.D., PRB, NINDB
Sheila Mitchell, M.D., O.A.D.C.S., NHI

Other Investigators : Heinz W. Berendes, M.D., PRB, NINDB
John L. Sever, M.D., PRB, NINDB

Cooperating Units : Laboratory of Technical Development, O.A.D.C.S., NHI

Man Years

Total	:	.33
Professional	:	.33
Other	:	.00

Project Description:

The primary objective of this study is to assess relationships between certain maternal variables and congenital heart-great vessel anomalies.

Additional objectives include investigating relationships between early signs of abnormality and the existence of definitive congenital heart lesions and determining the existence of congenital heart-vessel anomaly in conjunction with mental retardation as recorded in the eight-month psychological examination, the one-year summary records, four-year psychological examination, and seven-year neurological and psychological examinations.

To date, maternal parameters analyzed included age of gravida, parity, prior pregnancy outcome, prior and current health status, ABO blood group, current smoking pattern, and viral antibody status.

Study data was obtained from Collaborative Study records received by PRB from the onset of the Study (January 1959) through December 1964. These records provided 112 live and stillbirth cardiac cases for study out of a population pool of approximately 38,000. Analysis of an expanded Study cohort through

1965 with a population pool of approximately 55,000 providing additional cases is underway in anticipation that the additional cases will support earlier findings and perhaps provide further clues for identifying etiological relationships.

Major Findings:

There was a definite preponderance of mothers over 30 in the C-V Study group. Controlling for race, and removing cases with chromosomal aberrations, there were more white mothers in the 30 and over age group than expected at the .05 level. This trend is also noted among Negroes. There was a greater than expected number of gravida with systemic disease complications and prior pregnancy loss amongst the mothers of the cardiacs. A breakdown of these factors for greater specificity is pending.

Because the number of patients with each specific cardiac abnormality was small, specific associations between serological findings and clinical observations was not possible, although several interesting trends were noted. Further analysis with additional patients is under way.

A preliminary report on the 1964 cohort study was presented at the 1966 Annual Meeting of the Teratology Society.

Honors and Awards: None

Publications : None

Serial No. NDB-(CF)-63 PR/PN 1164
1. Perinatal Research Branch, NINDB
2. Section on Pediatric Neurology
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title : Early Signs as Predictors of Death and Neurological Abnormality Among Premature Infants Weighing 1000-2000 Grams

Previous Serial Number: Same

Principal Investigator: Joseph S. Drage, M.D., PRB, NINDB

Other Investigators : Karin B. Nelson, M.D., PRB, NINDB
Heinz Berendes, M.D., PRB, NINDB

Cooperating Units : None

Man Years

Total	:	.16
Professional	:	.08
Other	:	.08

Project Description:

A group of 720 single liveborn premature infants with birthweights of 1000-2000 grams has been prospectively studied relating the presence of specific neurological signs during the nursery period to neurological status at one year of age. Of the 720 infants, 485 were examined at one year, 159 died during the first year, and 76 were lost to follow-up. There were 101 neurologically abnormal infants among the 485 examined at one year. The first four PED-2's (Neonatal Pediatric Examinations) were reviewed for the presence or absence of early signs. Among the 720 infants, 78.2% received four or more PED-2 examinations while 100.0% of the abnormals and 94.8% of the normals received four or more examinations. Many of the deaths were in the first 24 hours of life, and most of the infants receiving zero, one, or two PED-2 examinations were deaths. A positive early sign was defined as the occurrence, on at least one examination, of the specific early sign being studied. Specific signs studied included cry, suck, palmar grasp, traction response, Moro reflex, eye movement, muscle tone, local convulsions, general convulsions, highest serum bilirubin, Coombs' test, procedures of resuscitation, etc. Each of these signs was considered separately, and those showing significant association with death and abnormal outcome were then combined. When three signs were considered in combination, the more that were positive the greater the association of neurological abnormality and death, and of neurological abnormality alone.

This study is now being up-dated on the entire study sample to include some 1400 cases.

Honors and Awards: None

Publications : None

Serial No. NDB (CF)-65 PR/PN 1271
1. Perinatal Research Branch, NINDB
2. Section on Pediatric Neurology
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Effects of Maternal Rubella as Evaluated in the One-Year-Old Child

Previous Title: Maternal Rubella and Pregnancy Outcome

Previous Serial Number: NDB (CF)-65 PR/ID 1271

Principal Investigators: Karin B. Nelson, M.D., PRB, NINDB
John L. Sever, M.D., PRB, NINDB

Other Investigators: Mary R. Gilkeson, PRB, NINDB

Cooperating Units: Section on Infectious Diseases

Man Years:

Total:	.33
Professional:	.25
Other:	.08

Project Description: A follow-up of pregnancies occurring during the 1964 epidemic of rubella is now underway. A hand review has been completed of all cases in which clinical rubella was reported in Study patients during the epidemic, and of all patients who reported exposure to rubella without clinical disease during the first trimester.

Records have been abstracted with regard to somatic measurements at birth, 4 months, 8 months, and 1 year; neurological and pediatric examinations at 4 months and 1 year; psychological evaluation at 8 months; certain motor milestones evaluated at 1 year; and interval medical history of illness, hospitalization, or medical consultation during the first year.

Of 56 women with clinical rubella during the first trimester, 12 had children who did not survive the newborn period (8 were therapeutic abortions, 1 a spontaneous abortion, 2 were stillborn and 1 a neonatal death); 8 were lost to study, one died at a year, and 35 were examined at one year of age. The late death and five other children (16.7% of the cases of known outcome at one year) were considered to be definite examples of the congenital rubella syndrome. Five of this six were diagnosed as such during the newborn period. An additional child had definite microcephaly; his inclusion would raise the rate of frank rubella defects to 19.4%.

Small heads were commoner in the clinical rubella first trimester group than in the group only exposed to rubella during the first trimester. This was true even excluding the children who were premature by birthweight, who were also more frequent in the clinical rubella group, and excluding all children who were considered to have the congenital rubella syndrome. There was a lowering of mean head circumference, and a smooth shift of the curve downward suggesting moderate as well as marked decreases in head size in the children whose mothers had had rubella.

A number of nonspecific abnormalities such as low birthweight, short stature at 1 year, inability to pull to standing by one-year (even excluding children premature by birthweight), edentulousness at one year, and somatic asymmetries were more frequent in the group of children whose mothers had clinical rubella during the first trimester of pregnancy.

Clinical rubella during the second and third trimesters of pregnancy seems also to have had some effect. In general, the frequencies of the defects mentioned above were less than with first trimester rubella, but more than with first trimester exposure alone.

An effort was made to compare the outcomes of cases exposed to rubella in the first trimester who did, and who did not, receive prophylactic gamma globulin after exposure. Analysis revealed that these two groups were so differently constituted by race as to be very difficult to compare usefully. A suspicion of socioeconomic and other differences made it seem unwarranted to consider a comparison of white patients only. In general, mortality figures were the same in the two groups, and the only clear-cut difference was that suspected hearing impairment occurred more frequently in children whose mothers had not received gamma globulin.

It is suggested by these preliminary observations that rubella infection in pregnancy may have an effect even where the classical congenital abnormalities are not present, and in cases not showing obvious acute congenital rubella of the newborn. These less specific effects are far less easy to express in single abnormality figures, but require consideration when the effect of rubella in pregnancy is appraised.

Further progress awaits serological testing of the 6000 women with no history of exposure of rubella. This is in progress but is a time-consuming job.

Honors and Awards: None

Publications: None

Serial No. NDB-(CF)-66 PR/PN 1335
1. Perinatal Research Branch, NINDB
2. Section on Pediatric Neurology
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title : Mortality and Morbidity Among Infants Weighing 1000-2000 Grams

Previous Serial Number: Same

Principal Investigator: Joseph S. Drage, M.D., PRB, NINDB

Other Investigators : Karin B. Nelson, M.D., PRB, NINDB
B. H. Williams, M.D., PRB, NINDB

Cooperating Units : None

Man Years

Total	.17
Professional	.08
Other	.08

Project Description:

A group of 720 liveborn infants, with birthweights ranging from 1000-2000 grams, has been studied regarding outcome within the first year of life. This group of 720 infants represents approximately 2% of the group of 35,000 single live births from which they were drawn.

Within the group of 720 infants, 485 were examined at one year of age, and of these 101 were considered to have definite neurological abnormality. There were 159 deaths during the first year of life. Thus, 260 of the 720 infants either died during the first year of life or were considered neurologically abnormal by examination at one year. There were 76 infants lost to follow-up and this represents 10% of the original 720 cases. Over 50% of the 159 deaths occurred during the first 24 hours and over 90% occurred during the first 28 days.

The 101 infants neurologically abnormal at one year were classified in the following way: isolated motor retardation, diplegia, hemiplegia, quadriplegia, monoplegia, athetosis, motor retardation with neurological signs insufficient for other diagnosis, and other (infants with neurological signs, but not fitting a specific diagnostic category). Congenital malformations were also monitored for this group.

Outcome at one year (death, abnormal, normal, and lost) was then tabulated within each 100-gram birthweight interval. In general for the 720 infants, as the birthweight increased, the percent of deaths decreased. For infants in jeopardy (dead or abnormal at one year), the same relationship held. The percent of lost cases within each 100-gram birthweight interval varied slightly. Study in Progress.

This study sample is currently being increased to include some 1400 infants.

Honors and Awards: None

Publications : None

Serial No. NDB-(CF)-66 PR/PN 1336
1. Perinatal Research Branch, NINDB
2. Section on Pediatric Neurology
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title : Effects on the Child of Convulsive Disorder in the Mother

Previous Serial Number: Same

Principal Investigator: Karin B. Nelson, M.D., PRB, NINDB

Other Investigators : None

Cooperating Units : None

Man Years

Total	:	.00
Professional	:	.00
Other	:	.00

Project Description: This project was discontinued.

Honors and Awards : None

Publications : None

Serial No. NDB (CF)-66 PR/PN 1337
1. Perinatal Research Branch, NINDB
2. Section on Pediatric Neurology
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: An Investigation into Relationships Between History of Signs, Symptoms and Behavior Early in Pregnancy and Pregnancy outcomes.

Previous Serial Number: Same

Principal Investigators: Lenore Bajda, M.D., PRB, NINDB
Rudolph Vollman, M.D., PRB, NINDB
Sarah H. Sledge, Ph. D., PRB, NINDB

Other Investigators: Laverne C. Edmondson, Statistical Assistant, PRB, NINDB.

Cooperating Units: None

Man Years

Total:	.08
Professional:	.08
Other:	.00

Project Description:

This study will look for meaningful associations between findings reported by Collaborative Project gravida in the interval histories during pregnancy (OB-3 and OB-8) and outcomes of pregnancy as noted on the newborn and 1-year diagnostic summaries and the 8-month and 4-year psychological examinations. The outcomes will also be considered in the light of prior pregnancy losses.

Study cohort to be used are Core gravida first trimester registrants (14 weeks or less from LMP) from onset of the Collaborative Project to January 1966, with single live-birth outcomes. The project has been in abeyance pending up-dating and completing of the data file.

Honors and Awards: None

Publications: None

Serial No. NDB (CF)-66 PR/PN 1338
1. Perinatal Research Branch, NINDB
2. Section on Pediatric Neurology
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: The Association of Mental Subnormality with Head Circumference, Congenital Malformations, and Other Conditions of the Newborn Term Infant

Previous Serial Number: Same

Principal Investigator: Lenore Bajda, M.D., PRB, NINDB

Other Investigator: Martin A. Mendelson, Ph.D., Department of Public Health, Washington, D.C.

Cooperating Units: Department of Public Health, Washington, D.C.

Man Years

Total:	.08
Professional:	.08
Other:	.00

Project Description:

The objective of this study is to determine the relationship between head size and certain other physical features taken on the child shortly after birth and at 1-year and indications of possible mental retardation as manifested by performance on the 8-month and 4-year Psychological Examinations; specifically, the scores on the mental scales, fine motor and gross motor scales. A study somewhat along these lines was made on the basis of retrospective data at the Mayo Foundation of the Mayo Clinic, Rochester, Minnesota by Drs. Edward J. O'Connell, Robert H. Felt and Gunner B. Stickler. Their study was reported in Pediatrics, 36:1, July, 1965. The objective of our study based on prospective data is similar to the objective formulated for the Mayo study in that it will be designed to determine whether there is a significant incidence in mental subnormality in CORE Study children; primarily in terms of physical features--head circumference, body length, and weight--and the relationships of these to scores on the 8-month Psychological Examination (controlling for gross diagnosis of outcome at the 1-year level). Project in abeyance pending up-dating of data file.

Honors and Awards: None

Publications: None

Serial No. NDB (CF)-66 PR/PN 1339
1. Perinatal Research Branch, NINDB
2. Section on Pediatric Neurology
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Sudden Unexpected Death

Previous Serial Number: Same

Principal Investigator: Joseph S. Drage, M.D., PRB, NINDB

Other Investigators: Toshio Fujikura, M.D., PRB, NINDB
Lon White, M.D., PRB, NINDB

Cooperating Units: None

Man Years

Total:	.16
Professional:	.08
Other:	.08

Project Description:

Some 207 cases of sudden death among 36,000 Collaborative Study children where the death occurred outside of a hospital have been reviewed regarding the cause. There were 90 cases autopsied where no cause of death was found. There were 34 deaths where the cause of death was known and 86 cases where the death was sudden and unexplained but no autopsy was performed.

The frequency distribution of the socioeconomic indices of the 90 cases of autopsied sudden unexplainable deaths was significantly lower than that of the index for all 36,000 study children. For the deaths of known cause, the frequency distribution of socioeconomic indices was essentially super-imposed on the distribution of the 36,000 study children.

The purpose of this study is to investigate the early neonatal course of these sudden unexplainable deaths for evidence of abnormality or instability which could differentiate this group from a group of controls matched for hospital sex, race, and birthweight. Data is being reviewed regarding the time of first breath, time of first cry, need for resuscitation, Apgar score at 1 and 5 minutes, staining of skin and umbilicus, need for special environmental conditions, temperature variation, abnormalities of cry, activity, respiration, color, feeding, and the presence of seizures. Laboratory data regarding ABO blood type, Rh type, lowest hemoglobin, highest bilirubin were also evaluated.

Study is still in progress.

Honors and Awards: None

Publications: None

Serial No. NDB (CF)-67 PR/PN 1509
1. Perinatal Research Branch, NINDB
2. Section on Pediatric Neurology
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: 1-Year Head Circumference in Relation to I.Q. at 4 Years

Previous Title: Head Circumference

Previous Serial Number: Same

Principal Investigator: Karin B. Nelson, M.D., PRB, NINDB

Other Investigators: Lon R. White, M.D., RP, CH
Heinz W. Berendes, M.D., PRB, NINDB
William Weiss, Office of Biometry, NINDB

Cooperating Units: Reproduction Program, National Institute of Child Health and Human Development

Man Years

Total:	.08
Professional:	.08
Other:	.00

Project Description:

A general association of small head size, short stature, and mental retardation has been remarked for almost 100 years. In 1965, investigators at the Mayo Clinic (O'Connell, Feldt, and Stickler, Pediatrics 36:62, 1965) presented the statement that non-institutionalized children older than 1 year with head circumferences two or more standard deviations below the mean were mentally retarded in 133 of 134 cases examined. Growth-retarded children of normal intelligence had heads appropriate to their sex and ages, not proportional to their heights. The conclusion reached was that a departure of two standard deviations below the mean head circumference suggested the diagnosis of mental subnormality with great confidence, without regard to body size.

The Mayo paper is cited frequently, but has never been confirmed by study of any other patient group. Because it would be of considerable value to be able to identify by such a handy measure as head size those children at high risk of mental subnormality, it would seem worthwhile to attempt to confirm or refute the stated relationship by the study of a large and consistently examined sample. The study for which the layout is given below proposes such an evaluation.

Layout

A. Cohort: Core cases, 1st study pregnancies, single births. Include only cases with 1 year exams undertaken when child was 50-54 weeks old, and for whom there are 4-year psychological examinations. Exclude for cohort all cases with definite cyanotic heart disease on PED-12.

B. Main Variables

1. Head circumference at 1 year ($\leq$ 41 cm., 42,43,44,..., 49,50,$\geq$ 51).

2. Body length at 1 year ($\leq$ 65 cm., 66,67,...,80, 81,$\geq$ 82)

3. Head circumference at 1 year ($\leq$ 43 cm., 44,45-46,47$\geq$ 48) by body length at 1 year ($\leq$ 69 cm., 70-72,73-77, $\geq$ 78)

C. Control Variables

1. Race (White, Negro only - no total)

2. Sex

3. Education of mother (0-8,9-11,12,$\geq$ 13)
(academic years only - vocational schools, etc., to be disregarded).

D. Outcome Variables

1. 4-year I.Q. ($<$ 70,70-79,80-119,$\geq$ 120)

2. Graham Block Sort (0-11,12-23,$\geq$ 24)

E. Tabulating Instructions

For each variable (B), obtain cross-tabulations against each outcome variable (D), Controlling simultaneously on Race (C1), Sex (C2), and Education of gravida (C3). Repeat, changing controls to Race (C1) and institution (C4). Repeat for both tabulations, substituting means and standard deviations for outcome variables, rather than obtaining grouped distributions.

Honors and Awards: None

Publications: None

Serial No. NDB (CF)-68 PR/PN 1627
1. Perinatal Research Branch, NINDB
2. Section on Pediatric Neurology
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Neuropsychological Outcome in Children Whose Mothers were Given Tetracycline During Pregnancy.

Previous Serial Number: None

Principal Investigator: Lawrence E. Gershon, M.D., PRB, NINDB

Other Investigators: None

Cooperating Units: None

Man Years

Total:	.35
Professional:	.30
Other:	.05

Project Description:

It was hypothesized that tetracycline may reduce the amount of bacterial interference so that utilization of amino acid for fetal development may be increased. It was also considered possible that this drug might interfere with intermediary metabolism and adversely affect the fetus. To determine the possible effects, a case listing of all those women reported to have received tetracycline was requested. The cases were hand reviewed and matched to controls by institution, race, sex, maternal age and parity.

It was found that the children of mothers who received tetracycline were, as a group, 5.1 Binet I.Q. points higher than their controls. The data, when subject to t test, had a p of .001. The results of this analysis are being prepared for publication.

We are also preparing to analyze the height and weight of these children and are awaiting a computer printout of the data.

Honors and Awards: None

Publications: None

Serial No. NDB (CF)-68 PR/PN 1628
1. Perinatal Research Branch, NINDB
2. Section on Pediatric Neurology
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Effects of Prenatal Protein Deprivation on Behavior and Brain Structure of Mice

Principal Investigators: John A. Churchill, M.D., PRB, NINDB
J. H. Carleton, M.D., PRB, NINDB
W. Lawrence Holley, M.D., PRB, NINDB

Other Investigators: None

Cooperating Units: None

Man Years

Total:	.3
Professional:	.2
Other:	.1

Project Description:

Previous studies have shown that deprivation of protein during pregnancy in rats results in full-term but small offspring with impaired ability on learning measures. There has also been suggestive evidence of microscopic structural differences in the brains of the study animals.

The present study was designed to replicate, in a certain strain of mice, the behavioral effects noted in the rats. After the mice have been tested for learning ability, the mice will be sacrificed and the brains examined with an electron microscope to determine structural changes, if any. The group of mice consists of approximately 50 mice in each of the following groups: mice born to female mice fed a high protein diet during gestation; mice born to female mice with a normal protein diet; and mice born to female mice with a protein-deficient diet during gestation.

The mice which have been tested to date have decreased learning abilities. None of the brains have been examined microscopically yet so there is no information concerning structural differences.

The study is still in progress at this time.

Honors and Awards: None

Publications: None

Serial No. NDB (CF)-68 PR/PN 1629
1. Perinatal Research Branch, NINDB
2. Section on Pediatric Neurology
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: The Effect of Maternal Hypertension on the Neuropsychological Outcome of the Child

Previous Serial Number: None

Principal Investigators: W. Lawrence Holley, M.D., PRB, NINDB
Heinz W. Berendes, M.D., PRB, NINDB
John A. Churchill, M.D., PRB, NINDB

Other Investigators: None

Cooperating Units: None

Man Years

Total:	.15
Professional:	.10
Other:	.05

Project Description:

Many investigators have studied the effects of hypertension in a pregnant woman. At the present time, there is still disagreement about the effects either to the mother or the offspring. This study attempts to verify what effect, if any, hypertension without proteinuria has on the neuropsychological outcome of the child.

Cases were obtained by selecting all single livebirths from the Collaborative Project study children, who had been given the Binet I.Q. at 4 years of age. The criteria for hypertension was a diastolic blood pressure of greater than 110 mm. Hg. Controls were chosen to have similar socio-economic index, sex, parity and race but who had no diastolic blood pressure greater than 90 mm. Hg.

The tabulation which has been completed, at this time, indicates that hypertension has no significant effect on the neuropsychological outcome of the child. We are reviewing the individual charts, at the present time, to exclude any other factors affecting the neuropsychological outcome of either the case or the control.

The study is in progress at this time.

Honors and Awards: None

Publications: None

Serial No. NDB (CF)-68 PR/PN 1630
1. Perinatal Research Branch, NINDB
2. Section on Pediatric Neurology
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: The Effect of Maternal Hypertension with Proteinuria on The Neuropsychological Outcome of the Child

Previous Serial Number: None

Principal Investigators: W. Lawrence Holley, M.D., PRB, NINDB
Heinz W. Berendes, M. D., PRB, NINDB
John A. Churchill, M. D., PRB, NINDB

Other Investigators: None

Cooperating Units: None

Man Years

Total:	.30
Professional:	.20
Other:	.10

Project Description:

There is general agreement that toxemia of pregnancy has unfavorable effects on the child. This relationship has never been fully defined except that children born to toxemic women have a greater incidence of prematurity. There have also been studies indicating central-nervous system impairment. This study relates toxemia (defined in this study as diastolic blood pressure greater than 110 mm Hg. with at least 3+ albuminuria) to neuropsychological deficits measured by the Bayley developmental scores at 8 months, the Binet I.Q. at 4 years of age, and a posturing scale at 12 months of age.

The study group and the controls included all single-liveborn children from the entire Collaborative Project who met the criteria; 127 cases and 127 controls were obtained.

The results show that children born to women with hypertension and proteinuria do have neuropsychological deficits when compared to "normotensive," albuminuria free controls. The impairment is independent of the effect of prematurity.

One finds a stunting of the children born to women with toxemia; that is, the infants have low birthweight for pregnancy duration. It is felt that this stunting reflects intrauterine deprivation because of protein loss in the urine with corresponding nutritional deficits because of poor placental circulation secondary to hypertention.

This study has been completed and is being prepared for publication.

Honors and Awards: None

Publications: None

Serial No. NDB (CF)-68 PR/PN 1631
1. Perinatal Research Branch, NINDB
2. Section on Pediatric Neurology
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Neuropsychologic Outcome of Children Whose Mothers Had Proteinuria During Pregnancy.

Previous Serial Number: None

Principal Investigators: Arthur L. Rosenbaum, M.D., PRB, NINDB
John A. Churchill, M.D., PRB, NINDB

Other Investigators: Zekin A. Shakhashiri, M.D., PRB, NINDB

Cooperating Units: None

Man Years

Total:	.25
Professional:	.20
Other:	.05

Project Description:

Animal experimentation has demonstrated a generally poor outcome for the newborn when the mother has been deprived a dietary protein during pregnancy. Offspring of protein deprived rats are smaller in size and have depressed learning abilities. Protein-calorie restriction in weanling animals has been shown to result in stunting, changes in brain composition, and specific neuronal abnormalities.

Less is known about the effect of maternal protein deprivation on the human fetus. The suggestion has been made that some babies born small for their gestational ages, such as twins, may have suffered protein impoverishment. Organ size in fetuses judged small for gestational age seem to be decreased.

Protein loss during pregnancy may have effects on the developing fetus similar to those of low protein intake. This study was designed to examine the effects of maternal proteinuria on psychological and neurological outcomes in the child.

The offspring of women with heavy proteinuria and without hypertension during the second half of pregnancy were matched with "non-proteinuric" control cases. 53 case pairs were thus selected, and the following outcome variables were studied:

A. Duration of Pregnancy
B. Birthweight
C. Bayley mental and motor scores given at 8 months of age
D. The Binet I.Q. given at 4 years of age
E. A rating scale for postural control observed at 1 year of age

The offspring of the 51 mothers with proteinuria (P) differed significantly from matched cases without proteinuria (C) in the Bayley Mental scores obtained when the children were 8 months of age, the posturing rating scale observed at 12 months of age, and the Binet I.Q. administered at 4 years of age. Neurologic abnormalities, other than the posturing scale, occurred in 5 offspring of proteinuric and in 1 of non-proteinuric mothers. There was no overall significant difference between the two groups in birthweight or duration of pregnancy. However, birthweights of all groups except the non-white female subjects were significantly lower than their matched controls, $p = <.05$, by Chi-Square analysis.

Paper has been approved and is being submitted for publication.

Honors and Awards: None

Publications: None

Serial No. NDB (CF)-68 PR/PN 1632
1. Perinatal Research Branch, NINDB
2. Section on Pediatric Neurology
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Neuropsychologic Outcome of Children Born Via the Occiput Posterior Birth Position

Previous Serial Number: None

Principal Investigators: Arthur Rosenbaum, M.D., PRB, NINDB
Lee Willerman, Ph. D., PRB, NINDB
John A. Churchill, M.D., PRB, NINDB

Other Investigators: None

Cooperating Units: None

Man Years

Total:	.30
Professional:	.25
Other:	.05

Project Description:

It is well known that there is an increased incidence of mortality and morbidity among children born via the OP birth position. This study was designed as a long-term neuropsychological follow-up evaluation of these children.

Approximately 200 cases of live-born babies delivered in the OP position were studied and compared with a group of children born via the OA position. All cases were from one of the institutions in the Collaborative Perinatal Research project. The two groups were then compared in relationship to the following outcome variables: a) Birthweight, b) Bayley mental and motor scores given at 8 months of age, c) The Binet I.Q. given at 4 years of age, d) Neurologic abnormalities evaluated at 1 year of age.

The above outcome variables were also studied by subdividing the entire group of OP births into the following categories: a) Spontaneous OP delivery, b) Mid-forceps rotation, c) Manual rotation, d) Length of time during labor the child remained in the OP position.

Analysis of the data is still in progress

Honors and Awards: None

Publications: None

Serial No. NDB (CF)-68 PR/PN 1633
1. Perinatal Research Branch, NINDB
2. Section on Pediatric Neurology
3. Bethesda, Maryland

PHS-NIH

Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Neuropsychologic Outcome of Children with Retinal Hemorrhages at Birth

Previous Serial Number: None

Principal Investigators: Arthur L. Rosenbaum, M.D., PRB, NINDB
John A. Churchill, M.D., PRB, NINDB

Other Investigators: None

Cooperating Units: None

Man Years

Total:	.30
Professional:	.20
Other:	.10

Project Description:

Retinal hemorrhages in the newborn occur in approximately 20% vertex births. Much work has been done to elucidate the etiology of these hemorrhages, but little is known about their significance in terms of long term follow-up. This study was designed to study the neuropsychologic outcome of children with retinal hemorrhages, and also the relationship between laterality of the hemorrhage and birth position.

Approximately 200 cases of retinal hemorrhage in the newborn were studied, and matched with "non-hemorrhage" controls. These matched pairs were then compared in relationship to the following outcome variables:
a) Birthweight, b) Bayley mental and motor scores given at 8 months of age, c) The Binet I.Q. given at 4 years of age.

The retinal hemorrhage cases were also reviewed in an attempt to analyze the possibility of a relationship between birth position and the eye in which the hemorrhage occurred.

The study is still in progress.

Honors and Awards: None

Publications: None

Serial No. NDB (CF)-68 PR/PN 1634
1. Perinatal Research Branch
2. Section on Pediatric Neurology
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Spastic Diplegia of Prematurity

Previous Serial Number: None

Principal Investigators: John A. Churchill, M. D., PRB, NINDB
Jack H. Carleton, M. D., PRB, NINDB
Heinz W. Berendes, M. D., PRB, NINDB

Other Investigators: None

Cooperating Units: None

Man Years

Total:	.10
Professional:	.05
Other:	.05

Project Description:

Spastic diplegia of prematurity is probably the commonest type of the cerebral palsies, occurring in approximately 10% of infants weighing less than 2000 gms. at birth. Previously, weight loss exceeding 10% in infants becoming spastic was observed. This observation was confirmed with PRB data.

12 cases of spastic diplegia of prematurity were matched with non-diplegic prematures. It was found that, in spite of the weight loss which should produce hemoconcentration, spastic prematures had significantly lower hematocrit values at approximately 38 hours from birth than did the control group. ($P < .01$) This fall in hematocrit suggests the possibility of internal hemorrhage which could be in the brain, at least in part.

A group of 25 premature infants who had died and whose brains were available for study were reviewed. It was found that a significantly high proportion of prematures with low hematocrit values had intracerebral hemorrhage. ($P < .002$)

This finding suggests the possibility that spastic diplegia of prematurity results from intracerebral hemorrhage, perhaps around the vena terminalis, at or soon after birth.

Study is still in progress.

Honors and Awards: None

Publications: None

Serial No. NDB (CF)-68 PR/PN 1635
1. Perinatal Research Branch, NINDB
2. Section on Pediatric Neurology
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Neuropsychologic Deficits in Children of Diabetic Mothers

Previous Serial Number: None

Principal Investigators: John A. Churchill, M.D., PRB, NINDB
Heinz W. Berendes, M.D., PRB, NINDB
Jean Nemore, R.N., B.A., PRB, NINDB

Other Investigators: None

Cooperating Units: None

Man Years

Total:	.20
Professional:	.10
Other:	.10

Project Description:

Pregnancy appears to intensify diabetes, and in some women the disease can be detected only when gravid. The ill effect of maternal diabetes mellitus on the outcome of pregnancy has been known in terms of high rates of fetal losses, neonatal deaths and congenital malformations. Whether intellectual deficits are associated with maternal diabetes remains uncertain.

This study is addressed to the question whether the neurologic and psychologic status of children born to diabetic mothers differs from that of children of non-diabetic women. In addition, the question is posed whether an effect, if found, could be attributed to diabetes directly or to a complication of the disease, such as acidosis or prematurity. Particular attention was directed toward the occurrence of acetonuria, since previous studies have shown that perinatal mortality is exceedingly high when diabetic acidosis occurs. Other studies have indicated that perinatal mortality is similar in both latent and florid diabetic states. Therefore, the neuropsychologic status of children born to mothers with mild and with severe diabetes was studied separately.

Cases for study were drawn from the Perinatal Study of the National Institute of Neurological Diseases and Blindness, the total number being

about 50,000 pregnancies. The study population included only pregnancies resulting in single, liveborn babies who had been given the Bayley mental and motor examination at eight months, or the Binet test at four years of age.

Patients who had diabetes were classified in accordance with the system of White. For the purpose of the present study, mothers who had Class A diabetes, including cases with abnormal glucose tolerance curve and gestation diabetes, were grouped separately from those who had diabetes of Classes B, C, D, E, and F (hitherto referred to as Class B+).

In addition to keto-acidosis of a degree considered to be clinically significant, the presence of acetonuria alone was noted. Diabetics were classified into Groups I, II and III depending upon whether acetonuria (or diacetic acid) were present, absent, or not determined, respectively.

Each diabetic case was matched for hospital of birth, race and sex with a single non-diabetic case. "Controls" were matched also for the exact or next lowest socioeconomic index value, the same or greater maternal age, and the same or nearest birth order.

Dependent variables studied were: a) Duration of pregnancy, b) Birthweight, c) Bayley mental and motor exams given at 8 months of age, d) The Binet I.Q. test given at 4 years of age, e) a rating scale for postural control observed at one year of age.

237 cases of maternal diabetes were studied.

The offspring of diabetic mothers differed significantly from matched non-diabetics in the Bayley mental and motor scores given at 8 months, the posturing rating scale observed at 12 months of age, and the Binet I.Q. administered at 4 years of age. Duration of pregnancy was significantly shorter in diabetics than in controls. Birthweight of diabetics, while greater, did not differ significantly from controls.

The frequency of other neurologic abnormalities was approximately equal in the diabetic and control groups.

Acetone positive diabetic cases showed significantly greater developmental deficits than their matched controls. Again, in the diabetics, duration of pregnancy was significantly shorter and birthweight was not significantly different than controls. Acetone negative diabetic cases did not differ from their controls in the neuropsychologic measures. Duration of pregnancy was shorter than controls, as was the case in acetonuric diabetics. However, birthweight of acetone negative diabetics was greater than their controls: $p < .05$.

Sacral defects, most of which were dimples and pilonidal sinuses were observed in a higher proportion of insulin-treated than untreated cases, the difference in frequency of cases in the groups being statistically significant; $P < .01$. The frequency of sacral defects in offspring of diabetic mothers given no insulin differed little from that of the non-diabetic "control" cases.

In conclusion, maternal diabetes mellitus during gestation was found to have an adverse effect on neuropsychologic attributes of children. Deficits were observed in the Bayley Scale measured at 8 months of age, posturing factors derived from neurologic examination given at 12 months of age, persisting to affect the Binet I.Q. at 4 years of age. Of singular importance was the finding that diabetes accompanied by acetonuria was associated with the adverse effects on the fetus, but no deficits were found in the offspring of diabetic mothers free of acetonuria.

This paper was presented on March 14, 1968 at a weekly seminar at the University of Washington Medical School, Seattle, Washington.

This paper will be submitted to American Journal of Obstetrics and Gynecology in the near future.

Honors and Awards: None

Publications: None

Serial No. NDB (CF)-68 PR/PN 1636
1. Perinatal Research Branch, NINDB
2. Section on Pediatric Neurology
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: The Effect of Head Position at Birth on WISC Verbal and Performance I.Q.

Previous Serial Number: None

Principal Investigator: John A. Churchill, M. D., PRB, NINDB

Other Investigator: Lee Willerman, Ph.D., PRB, NINDB

Cooperating Units: None

Man Years

Total:	.25
Professional:	.20
Other:	.05

Project Description:

To test the hypothesis that head position at birth is related to superiority of (WISC) Verbal or Performance I.Q., head position at birth was determined for 212 Ss, including 95 sets of siblings born at Henry Ford Hospital, Detroit, Michigan. Children who were born Occiput Left (OL); that is, where the head was situated with the occiput in the left half of the maternal pelvis during delivery, were compared to children born Occiput Right (OR) for differences in WISC Verbal and Performance I.Q. The results indicated that children born OR had significantly lower Verbal I.Q. than Performance I.Q. ($p < .01$). When same-sexed sibs were compared, it was found that the OR sib more frequently had a higher Performance I.Q. than his mate ($p < .05$); there was also a trend which suggested that the OL sib had a higher Verbal I.Q. than his OL mate. The results were interpreted as supportive of the hypothesis that birth position is related to superiority of Verbal or Performance I.Q., and as suggesting that by the time of birth, lateralization of Verbal and performance function has already occurred.

An article has been accepted for publication.

Honors and Awards: None

Publication: Churchill, J.A., Willerman, L., Grisell, J., and Ayers, M.: The Effect of Head Positions at Birth on WISC Verbal and Performance I.Q. To be published in Psychol. Rev.

Serial No. NDB (CF)-68 PR/PN 1637
1. Perinatal Research Branch, NINDB
2. Section on Pediatric Neurology
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Relationship of Maternal Biliary Disease to I.Q. of the Offspring

Previous Serial Number: None

Principal Investigators: John A. Churchill, M.D., PRB, NINDB
Heinz W. Berendes, M.D., PRB, NINDB

Other Investigators: None

Cooperating Units: None

Man Years

Total:	.04
Professional:	.02
Other:	.02

Project Description:

In a previous study, the investigators had demonstrated significantly lower I.Q.'s of the children whose mothers had gall bladder disease when compared to a control group whose mothers did not have gall bladder disease. This study was designed for the purpose of confirming these findings with PRB data.

A listing was obtained of all cases indexed "Abdominal Operation" where the child had been given the 4-Year Psychological Examination. Out of this group, there were 98 cases of definite gall bladder disease. Six were second study pregnancies. One child was mongoloid, so the case was discarded. One child had focal motor epilepsy and was excluded; and one could not be matched for a control (this case also had diabetes). In each one of the cases, the presence of cholecystectomy was ascertained. There were 54 white patients with well-verified gall bladder disease; 3 problematic (2 had pancreatitis and 1 was a very peculiar case in that one couldn't be sure that she had gall bladder disease. She had had encephalitis, meningitis, was legally blind, had had an appendectomy, an episode of so-called gall bladder disease with cholecystectomy, sensitivity to sunlight in the form of a rash); 26 cases were Negro, 3 cases Puerto Rican. The cases were matched for institution, race, sex, S-E Index, maternal age, and birth order. Two controls had to be disqualified and others chosen because one child had congenital heart disease, another focal cerebral seizures.

The mean difference in I.Q. between the cases and their controls was 9 points, $p < .002$. Excluding the pancreatitis cases, the probability level was less than .001. The Negro group was not statistically significant in I.Q. difference.

Among the six women with gall bladder disease who had a first and second study pregnancy, the 2nd child had a lower I.Q. in each case. The mean difference was 6.8; $p < .01$. This suggests that duration of the disease may have a bearing upon the problem.

Maternal age and parity tend to be higher for those with lower I.Q.'s. The S-E Index was not significantly different.

One interesting observation was that the mothers with Italian heritage had higher I.Q. children than the others. An explanation is that the Italian mother, who has gall bladder disease, may get along fine because she uses a great deal of olive oil which is high in linoleic acid. Fish are also very high in linoleic acid.

The study is still in progress.

Honors and Awards: None

Publications: None

Serial No. NDB (CF)-68 PR/PN 1638
1. Perinatal Research Branch, NINDB
2. Section on Pediatric Neurology
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Relationships of Maternal Amino Acid Blood Levels to Fetal Development

Previous Serial Number: None

Principal Investigators: John A. Churchill, M.D., PRB, NINDB
Kamran S. Moghissi, M.D., F.A.C.O.G., Wayne State University, Detroit, Michigan
Charles Frohman, Ph.D., Lafayette Clinic, Detroit, Michigan

Other Investigators: None

Cooperating Units: Wayne State University, Detroit, Michigan
Lafayette Clinic, Detroit, Michigan

Man Years

Total:	.05
Professional:	.04
Other:	.01

Project Description:

In previous reports on relationships between low birthweight and intelligence, the suggestion was made that maternal nutritional deficiencies may produce intrauterine stunting and impair brain development of the fetus. Protein deprivation in pregnant rats was found to result in offspring with decreased birthweight and poor learning abilities when tested as adults.

This study was designed to investigate the effects of protein deprivation during human gestation as reflected in relationships between maternal blood levels of free alpha amino acids and infant birthweight, length and cranial volume. Controlling and assessing diets of pregnant women is difficult; hence, other measures of nutrient supply were sought; specifically, blood proteins and amino acids. The transfer of maternal amino acids to the fetus is known to be free and proportional.

All patients selected for study were admitted to the Wayne State University Department of Gynecology and Obstetrics at Hutzel Hospital in Detroit, Michigan.

All mothers were Negro and were in Social Class V, according to the Hollingshead-Redlich Scale. Nutritional assessments were made by a dietician who based amounts of nutrients ingested on 24-hour recalls of food eaten. Two groups were studied, those with protein intakes greater than 70 gm. and those with less than 50 gm.

Twenty ml. of oxalated blood were obtained between the 32nd and 34th weeks and again between the 34th and 36th weeks of gestation. Total alpha amino acid determinations were performed. Birthweights and lengths were recorded.

Using the means of the measurements, cranial volume was calculated by the formula V=0.52 x (LxBxH)-P; where L, B and H represent occipitofrontal, bi-parietal and porion diameters, respectively. P is an estimate of the volume contributed by scalp and skull thickness, which is 140 for neonatal males and 125 for females.

The mean amino acid value of the group of 64 term cases was found to be 3.992 mg./100ml. For analysis, cases with amino acid levels over 4.0 mg./100ml., called high, were compared to cases with amino acid levels less than 4.0 mg./100ml., called low.

The mean birthweight of infants whose mothers had high amino acid levels was 3.43 kg. Mothers with low amino acid levels had babies with a mean birthweight of 3.06 kg. ($t=1.539$, $p<.005$). However, duration of pregnancy was not significantly different between these groups.

The mean cranial volume associated with high amino acid levels was 472 cc.; whereas, the cranial volume of the low amino acid group was 426.2 cc. ($t=2.9379$, $p<.003$).

Neither birthweight, cranial volume nor fetal length were significantly related to the estimated dietary intake of protein or to blood albumin levels.

In summary, a significant relationship has been established between maternal blood amino acid levels during pregnancy and infant weight and cranial volume. No clear relationship could be established between estimated dietary intakes and either the status of the infant or maternal amino acid values. These data suggest that maintenance of high maternal blood amino acid levels during pregnancy may be important in reducing the incidence of low birthweight babies.

Study is in final preparation for publication.

Honors and Awards: None

Publications: None

Serial No. NDB (CF)-68 PR/PN 1639
1. Perinatal Research Branch, NINDB
2. Section on Pediatric Neurology
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Neuropsychologic Deficits in Children Whose Mothers Had Episodes of Acetonuria

Previous Serial Number: None

Principal Investigators: John A. Churchill, M.D., PRB, NINDB
Heinz W. Berendes, M.D., PRB, NINDB

Other Investigators: None

Cooperating Units: None

Man Years

Total:	.20
Professional:	.10
Other:	.10

Project Description:

Previously, it was found that the I.Q. of offspring of acetonuric diabetic mothers was lower than the I.Q. of children whose diabetic mothers were free of acetonuria. The question then is whether the presence of acetonuria in the mother was associated with deficits in intellectual function.

290 cases were found where the mother had acetonuria on 1 or more prenatal visits and where the child had had the Binet I.Q. test. The cases were matched with controls by institution of birth, race, sex, S. E. Index, maternal age, and parity. The mean I.Q. of controls was 97.1 while that of acetonuric cases was 93.6. The group means were found to be statistically significant, t was 3.3094, p was less than .0005. Differences relating to sex of the child were found which are being investigated further.

This Study is still in progress.

Honors and Awards: None

Publications: None

Serial No. NDB (CF)-68 PR/BS 1640
1. Perinatal Research Branch
2. Section on Behavioral Sciences
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Factors Related to Performance on Selected Items of the Four-Year Psychological Battery

Previous Serial Number: None

Principal Investigator: Jaswant Khanna, Ph. D., University of Tennessee

Other Investigators: Joseph Weber, Office of Biometry, NINDB
Robert Illardi, Ph. D., University of Tennessee
Sarah H. Sledge, Ph. D., PRB, NINDB

Cooperating Units: University of Tennessee
Office of Biometry, NINDB

Man Years:

Total:	.2
Professional:	.2
Other:	0

Project Description:

Objectives: To relate certain sociological, obstetrical, pediatric and overall psychometric characteristics of study children to performance on specific test items in the four-year psychology battery. Some anticipated results would be to distinguish between response patterns of whites and Negroes; identify test items which are most sensitive to biological variables and to social variables; and to identify items most closely related to total score as in the traditional model of item analysis.

Methods: Thirty descriptive variables in summary form are to be related to pass-fail on 61 response variables including Stanford-Binet items, concept formation items and fine and gross motor items for all children who have been evaluated at four years of age.

Status: Specifications are now being written for computer processing of this data.

Honors and Awards: None

Publications: None

Serial No. NDB (CF)-68 PR/BS 1641
1. Perinatal Research Branch
2. Section on Behavioral Sciences
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Fetal Head Position and Intelligence

Previous Serial Number : None

Principal Investigator: Dr. Lee Willerman, PRB, NINDB

Other Investigator: Dr. John A. Churchill, PRB, NINDB

Cooperating Unit: Section on Pediatric Neurology, PRB, NINDB

Man Years:

Total:	.45
Professional:	.40
Other:	.05

Project Description:

Objectives: From hospital records at Boston Lying-in, head position during birth and whether forceps were applied during delivery was determined for 213 children who had been given the WISC at seven years of age and the Stanford-Binet IQ test at four. The results indicated that children whose occiputs were situated in the right anterior quadrant of the maternal pelvis during delivery (ROAs) had significantly lower Stanford-Binet IQs than Ss whose occiputs were situated in the left anterior quadrant of the maternal pelvis (LOAs). This relationship was observed despite the application of forceps. The WISC similarly revealed a significantly higher Verbal IQ among LOAs than ROAs, but only in those delivered without forceps. No differences in Performance IQ were observed. The implications of these findings are discussed in terms of presumptive perinatal trauma and psychological functioning.

Willerman, L. & Churchill, J. A. Relationship of Fetal Head Position and Intelligence, currently before the NIH Publications Review Board

Honors and Awards: None

Publications: None

Serial No. NDB (CF)-68 PR/BS 1642
1. Perinatal Research Branch
2. Section on Behavioral Sciences
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Maternal Pelvic Size and Intelligence

Previous Serial Number: None

Principal Investigator: Dr. Lee Willerman, PRB, NINDB

Other Investigators: Dr. J. A. Churchill, PRB, NINDB
Dr. A. Rosenbaum, PRB, NINDB

Cooperating Unit: Section on Pediatric Neurology, PRB, NINDB

Man Years:

Total:	.40
Professional:	.35
Other:	.05

Project Description:

Objectives: The purpose of this project is to explore possible relationships between clinical obstetric estimations of maternal pelvic inadequacy and intellectual impairment in the offspring.
Stanford-Binet IQs of 287 vertex births whose mothers were coded as having upon clinical examination, either borderline or contracted pelves, were compared on IQ to a sample of 243 children whose mothers had adequate pelves. The finding indicated that women coded as having borderline or contracted pelvic outlets, as compared to those coded as adequate, had children with significantly more frequent low IQs ($IQ \leq 85$). Clinical estimates of inadequate pelvic inlet or mid pelvis regions were not associated with significantly more frequent low IQs. These results have been analyzed and a paper is currently being prepared for publication.

Honors and Awards: None

Publications: None

Serial No. NDB (CF)-68 PR/BS 1643
1. Perinatal Research Branch
2. Section on Behavioral Sciences
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Bayley Scores, 4-Year Intelligence and Socioeconomic Index

Previous Serial Number: None

Principal Investigator: Dr. Lee Willerman, PRB, NINDB

Other Investigator: Dr. Sarah H. Sledge, PRB, NINDB

Cooperating Units: None

Man Years:

Total:	.35
Professional:	.30
Other:	.05

Project Description:

Objectives: The purpose of this project is to describe the fate of developmentally retarded and advanced children as measured by the Bayley Scale of Infant Development. This study involves the Bayley scores of approximately 3600 white children. Preliminary analysis of 3000 children indicates that the four-year IQ of the children in the lowest quartile on the Bayley Motor Scale depends strongly on the socioeconomic class of the child. The higher the socioeconomic status, the less impaired the child. In contrast, in children scoring in the upper quartile on the Bayley Motor Scale, there is little association between socioeconomic status and IQ. Other findings are that children in the lowest Bayley Motor quartile have significantly lower IQ when compared to those in the upper quartile. Of interest also is the finding that in this sample of females, no child who later earned an IQ less than 80 (n=18) obtained an 8-month Motor Score above the mean for the population. This study is still in progress and data on the 8-month Mental scores are soon to be evaluated.

Honors and Awards: None

Publications: None

Serial No. NDB (CF)-68 PR/BS 1644
1. Perinatal Research Branch
2. Section on Behavioral Sciences
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1,1967 through June 30, 1968

Project Title: Maternal Pelvic Size and Neurological Outcome at Seven Years

Previous Serial Number: None

Principal Investigator: Dr. Lee Willerman, PRB, NINDB

Other Investigator: Dr. J. A. Churchill, PRB, NINDB

Cooperating Unit: Section on Pediatric Neurology, PRB, NINDB

Man Years:

Total:	.25
Professional:	.20
Other:	.05

Project Description:

Objectives: The purpose of this project has been to explore the relationship of small maternal pelvic size to neuropsychological outcome in the child. This study was based on a sample of 213 vertex births. As part of the Collaborative Perinatal Research Project, these children had received a psychological examination at seven years of age.

Major Findings: The results indicated that children born of small pelvis mothers, as compared to children born of large pelvis mothers, had significantly lower Wechsler Intelligence Scale for Children (WISC) Verbal IQ, but not significantly lower Performance IQ. Children born of these small pelvis mothers who had been delivered by forceps made more errors on the Tactile Finger Recognition Test than those children of large pelvis mothers who were delivered by forceps. Also, all children delivered by forceps made poorer scores on the Bender-Gestalt test than those delivered without forceps.

Willerman, L. & Churchill, J. A. Maternal Pelvic Size and Neuropsychological Outcome at Seven Years, currently before the NIH Publications Review Board.

Honors and Awards: None

Publications: None

Serial No. NDB (CF)-63 PR/EG 1173
1. Perinatal Research Branch
2. Section on Epidemiology and Genetics
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: A Study of Socioeconomic, Medical and Genetic Factors in Major Congenital Malformations

Previous Serial Number: Same

Principal Investigator: Dr. N.C. Myrianthopoulos, PRB, NINDB

Other Investigators: Dr. C. Chung, School of Public Health, University of Hawaii

Cooperating Units: None

Man Years

Total:	.05
Professional:	.05
Other:	.00

Project Description:

This is a continuation of a project to study the relation of medical and genetic factors to major congenital malformations. The first phase of the study was based on 593 cases of live births and fetal deaths with malformations and 1,186 controls drawn from a total of 35,941 births and fetal deaths. The malformations included anencephaly, polydactyly, cleft palate and/or harelip, spina bifida, and meningocele, congenital heart defects and hypospadias. The results of this phase have been published.

In the second phase the plan is to utilize the complete cohort of the Collaborative Study to investigate especially those relationships which have been shown to be significant in the preliminary study. A request for data output is now being prepared.

Honors and Awards: None

Publications:

Chung, C.S. and Myrianthopoulos, N.C.: Racial and prenatal factors in major congenital malformations. Am. J. Hum. Genet. 20:44-60, 1968.

Serial No. NDB (CF)-63 PR/EG 1174
1. Perinatal Research Branch
2. Section on Epidemiology and Genetics
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Birthweight in Relation to Selected Socioeconomic Variables

Previous Serial Number: Same

Principal Investigator: Dr. N.C. Myrianthopoulos, PRB, NINDB

Other Investigators: Dr. Joshua Lederberg, Stanford University

Cooperating Units: None

Man Years

Total:	.10
Professional:	.05
Other:	.05

Project Description:

This is a continuation of a study to relate birthweight to socioeconomic and medical variables. The results of the first part of the Study have already been published. In the second part the plan is to compare children in the 100th percentile of birthweight with children in the 50th percentile of birthweight and children of diabetic mothers, in terms of several socio-economic, biological and medical variables. A magnetic tape with all the necessary data has been prepared and analysis is now in progress.

Honors and Awards: None

Publications:

Naylor, A.F. and Myrianthopoulos, N.C.: The relation of ethnic and selected socioeconomic factors to human birthweight. Ann. Hum. Genet. 31:71-83, 1967.

Serial No. NDB (CF)-63 PR/EG 1175
1. Perinatal Research Branch
2. Section on Epidemiology and Genetics
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Determination of the Zygosity of Twins Born to Mothers in the Collaborative Study

Previous Serial Number: Same

Project Coordinator: Dr. N.C. Myrianthopoulos, PRB, NINDB

Cooperating Units: All Institutions participating in the Collaborative Study

Man Years

Total:	.15
Professional:	.15
Other:	.00

Project Description:

This is a continuing project to determine the zygosity of twins born to Study mothers. This determination is basic and vital to any subsequent studies using twins. Twin zygosity is determined by comparison of sex, placentation, blood groups, and finger and palm prints. This information is forwarded by all Institutions to the Section on Epidemiology and Genetics where it is classified and analyzed by special methods. The results are kept on file and are available to anyone wishing to engage in twin research. In progress.

Honors and Awards: None

Publications: None

Serial No. NDB (CF)-63 PR/EG 1177
1. Perinatal Research Branch
2. Section on Epidemiology and Genetics
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Genetic and Socioeconomic Factors in Early and Late Fetal Death

Previous Serial Number: Same

Principal Investigator: Dr. N.C. Myrianthopoulos, PRB, NINDB

Other Investigators: Dr. A.F. Naylor, PRB, NINDB
Dr. Herman Slatis, Michigan State University

Cooperating Units: None

Man Years

Total:	.10
Professional:	.10
Other:	.00

Project Description:

This is a continuation of a retrospective study of gravidae whose first study pregnancy terminated in early or late fetal death. The objective is to determine what effect do genetic and socioeconomic factors have on pregnancy wastage and if a distinction can be made etiologically between early and late fetal deaths. A computer program produced the records of 1,877 early and late fetal deaths and matched them with such study variables as prior pregnancy history of mother, parity, socioeconomic factors, and history of medications and diseases. A discriminant function analysis is now being designed with the statistical help of the Office of Biometry.

Honors and Awards: None

Publications: None

Serial No. NDB (CF)-63 PR/EG 1184
1. Perinatal Research Branch
2. Section on Epidemiology and Genetics
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Population Dynamics of Tay-Sachs Disease

Previous Serial Number: Same

Principal Investigator: Dr. N.C. Myrianthopoulos, PRB, NINDB

Other Investigators: Dr. Stanley Aronson, State University of New York

Cooperating Units: State University of New York

Man Years

Total:	.20
Professional:	.10
Other:	.10

Project Description:

This is a continuation of a study to determine whether differential fertility favoring the Jewish heterozygote can account for the 100-fold higher frequency of Tay-Sachs disease and the gene responsible for it among the Jewish compared with non-Jewish population in the U.S. Evidence for selective advantage of the heterozygote was found in the first part of the study (Am. J. Hum. Genet. 18:313-327, 1966). The plan in the second part is to investigate whether or not such advantage can be demonstrated in other sphingolipidoses, to study the demography of these disorders and to determine whether resistance to tuberculosis or some other infectious disease confers a selective advantage to the heterozygote.

Honors and Awards: None

Publications:

Aronson, S.M., Herzog, M.I., Brunt, P.W., McKusick, V.A., and Myrianthopoulos, N.C.: Inherited neurologic diseases of Ashkenazic Jewry: Demographic data suggesting non-random gene frequencies. Trans. Amer. Neurol. Ass. 117-121, 1967.

Serial No. NDB (CF)-65 PR/EG 1274
1. Perinatal Research Branch
2. Section on Epidemiology and Genetics
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Genetic Bases of Neonatal Reflexes

Previous Serial Number: Same

Principal Investigator: Dr. A. F. Naylor, PRB, NINDB

Other Investigators: Dr. N. C. Myrianthopoulos, PRB, NINDB

Cooperating Units: None

Man Years:

Total:	.14
Professional:	.10
Other:	.04

Project Description:

The validity of regarding the suck, rooting and other neonatal reflexes as definite genetic entities is under study. Cases involving loss of single reflexes without evidence of hypoxia or other trauma may be genetically based. Such cases are being sought.

Examination and evaluation of the computer output and case abstracts available at the time of the last annual report indicates the nature of further work needed to bring the project to a first stage of completion. A cohort free of observations concomitant with reflex weakness or absence (anoxia, respiratory disease, prematurity, etc.) must be selected. By looking in such a healthy baby population for individuals with absent reflexes some limits can be placed on frequency of loss due to genetic variation. Whereas the first analyses utilized half the PRB data, the new work will be done on essentially the complete files.

Honors and Awards: None

Publications: None

Serial No. NDB (CF)-65 PR/EG 1275
1. Perinatal Research Branch
2. Section on Epidemiology and Genetics
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Study of Family Size with Respect to Rh Blood Type and Other Variables

Previous Serial Number: Same

Principal Investigator: Dr. A. F. Naylor, PRB, NINDB

Other Investigators: Dr. N. C. Myrianthopoulos, PRB, NINDB

Cooperating Units: None

Man Years:

Total:	.02
Professional:	.02
Other:	.00

Project Description:

The project will re-examine the suggestion made by Glass in 1950 that fetal loss in Rh negative women may actually be over-compensated for in a population practicing birth control, which may be lifted when incompatibility loss occurs. Information on the Rh type of gravidae, previous incompatibility complications, family planning practices and race will be related to age-corrected family sizes of gravidae.

This project has been largely inactive but will be accelerated later this year.

Honors and Awards: None

Publications: None

Serial No. NDB (CF)-65 PR/EG 1276
1. Perinatal Research Branch
2. Section on Epidemiology and Genetics
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Sequential Aspects of Occurrence of Spontaneous Abortion in Family Histories

Previous Serial Number: Same

Principal Investigator: Dr. A.F. Naylor, PRB, NINDB

Other Investigators: Dr. Dorothy Warburton, College of Physicians and Surgeons of Columbia University

Cooperating Units: None

Man Years

Total:	.40
Professional:	.30
Other:	.10

Project Description:

Because the tape files of interest in this project are nearly completed and because certain kinds of bias that have been detected in the data can be more completely overcome in updated files, all previous computer programs and resulting analyses are being rerun.

Statistical analyses of OB-2 data indicate that, in part at least, the increasing risk of spontaneous abortion with age of mother is real and not explained by spurious statistical effects of reproductive compensation. A new type of computer tabular output has strengthened the arguments. With this new evidence added and updated figures entered the existing manuscript should be ready for submission.

Another phase of this project has been reported in Am. J. Obstet. Gynec. 97:931-935, 1967.

The programming effort is essentially complete. However, the output has indicated that gravidae who aborted soon after registration of the study pregnancy have failed to complete an OB-2 history. An effort will be made to overcome this bias by use of Gen-5 and repeat pregnancy OB-2 information.

Honors and Awards: None

Publications: None

Serial No. NDB (CF)-67 PR/EG 1510
1. Perinatal Research Branch
2. Section on Epidemiology and Genetics
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: The Study of Maternal Effects in the Production of Congenital Malformations

Previous Serial Number: Same

Principal Investigator: Dr. N.C. Myrianthopoulos, PRB, NINDB

Other Investigators: None

Cooperating Units: None

Man Years

Total:	.05
Professional:	.05
Other:	.00

Project Description:

This is a study to determine the extent to which maternal factors are involved in the production of congenital malformations, and to single out those malformations and conditions of the newborn in which the role of maternal factors, genetic and environmental, appears to be deciding. The GEN. 5-8 will be used to obtain a history of outcome of prior pregnancies, in families in which half-siblings are present. Study pregnancies will also be included. These will be screened for occurrences of congenital malformations and other conditions among children by different fathers. Genetic and socioeconomic correlations will be made. Since the number of cases which would yield the desired information is expected to be small, a request for computer output for an initial listing has been deferred until data on the complete cohort become available.

Honors and Awards: None

Publications: None

Serial No. NDB (CF)-67 PR/EG 1511
1. Perinatal Research Branch
2. Section on Epidemiology and Genetics
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: A Comparative Study of Reporting of Various Congenital Malformations

Previous Serial Number: Same

Principal Investigators: Dr. N.C. Myrianthopoulos, PRB, NINDB
Sylvia Hay, Dental Health Center, PHS, San Francisco, California

Other Investigators: None

Cooperating Units: Congenital Anomalies Section, Epidemiology Branch, Dental Health Center, PHS, San Francisco, California

Man Years

Total:	.20
Professional:	.10
Other:	.10

Project Description:

The purpose of this study is to assess the quality of the reporting of cleft lip and palate as well as other congenital malformations, on birth certificates. A review of birth certificates of children with clefts born in the Collaborative Study from 1962 to 1965 showed that only 46.4 percent contained information about the clefts and none contained information about a specific defect, cleft gum. Six children with cleft gum from the Medical College of Virginia have been examined for persistence of the clefts in childhood, and x-rays were taken to determine whether a bone abnormality underlies the anomaly of the soft tissue. The results are not yet available.

Honors and Awards: None

Publications: None

Serial No. NDB (CF)-67 PR/EG 1512
1. Perinatal Research Branch
2. Section on Epidemiology and Genetics
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Relationship of Maternal ABO and Rh Blood Groups to Pregnancy Outcome and Infant Survival

Previous Serial Number: Same

Principal Investigators: Dr. N. C. Myrianthopoulos, PRB, NINDB
Dr. Bernice H. Cohen, Johns Hopkins University
Jeffrey E. Sayre, Johns Hopkins University

Other Investigators: None

Cooperating Units: Department of Chronic Diseases, The Johns Hopkins University School of Hygiene and Public Health

Man Years

Total:	.15
Professional:	.15
Other	.00

Project Description:

This is a continuation of a study to examine the role of ABO and Rh Blood groups in the risk of fetal, neonatal and infant mortality, to investigate blood group associations other than incompatibility and to determine any differences by ethnic, socioeconomic and maternal variables. Computer output was obtained with information concerning gravidae and study children (including fetal deaths) of the 1959-64 cohort, consisting of obstetric and reproductive history, laboratory data, gestational age, sex of offspring, birthweight, ABO and Rh types and socioeconomic index scores. A first round of analysis indicated that specific types of information were required by finer subdivisions, and further computer output has been requested. Analysis is in progress.

Honors and Awards: None

Publications: None

Serial No. NDB (CF)-67 PR/EG 1513
1. Perinatal Research Branch
2. Section on Epidemiology and Genetics
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: A Genetic Study of Congenital Polycystic Kidney

Previous Serial Number: Same

Principal Investigator: Dr. N. C. Myrianthopoulos, PRB, NINDB

Other Investigator: None

Cooperating Units: None

Man Years

Total:	.05
Professional:	.05
Other:	.00

Project Description:

The purpose of this project is to study the formal genetics of congenital polycystic kidney and to clarify the relationship of this fatal malformation with the unilateral polycystic kidney of the adult which is compatible with life. Thirty-four children who died of pathologically verified congenital polycystic kidney have been identified. This gives a birth incidence of about 1 in 1,650 births. The frequency of this malformation appears to be significantly higher in Negro than in White babies. Family histories are now being reviewed and will be followed by intensive field work and examinations of close relations. Segregation analysis will be employed to determine the mode of inheritance.

Honors and Awards: None

Publications: None

Serial No. NDB (CF)-67 PR/EG 1514
1. Perinatal Research Branch
2. Section on Epidemiology and Genetics
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Record Linkage of Relatives Registered in the Collaborative Study

Previous Serial Number: None

Principal Investigator: Dr. A. F. Naylor, PRB, NINDB

Other Investigators: Dr. N. C. Myrianthopoulos, PRB, NINDB

Cooperating Units: None

Man Years:

Total:	.10
Professional:	.05
Other:	.05

Project Description:

Since the Gen. 5-8 files are practically complete on computer tape, a listing of 3505 cards with codes indicating presence of relatives of the mother or father of the baby in the study has been requested and delivered. The number is a gratifying 6482. This list is being sampled for quality testing. At present, indications are that the card codes are highly reliable and the relatives reported have been almost always identified. However, reciprocal reporting of related gravidae is inexplicably infrequent.

The present results indicate that the Collaborative Study contains a large body of usable information of great value to genetic studies.

Honors and Awards: None

Publications: None

Serial No. NDB (CF)-67 PR/EG 1515
1. Perinatal Research Branch
2. Section on Epidemiology and Genetics
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Rh Hemolytic Disease in Negro and White Infants

Previous Serial Number: None

Principal Investigator: Dr. A. F. Naylor, PRB, NINDB

Other Investigators: None

Cooperating Units: None

Man Years:

Total:	.00
Professional:	.00
Other:	.00

Project Description:

This is intended to check a report that high Rh antibody levels have smaller morbid effects in Negro than in White babies, although this is not true for ABO antibodies.

This new project is not yet being actively pursued.

Honors and Awards: None

Publications: None

Serial No. NDB (CF)-67 PR/EG 1516
1. Perinatal Research Branch
2. Section on Epidemiology and Genetics
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Size of Placenta in Relation to Mother-Fetus Antigenic Difference

Previous Serial Number: None

Principal Investigators: Dr. Dorothy Warburton, College of Physicians and Surgeons of Columbia University
Dr. A. F. Naylor, PRB, NINDB

Other Investigators: Dr. Toshio Fujikura, PRB, NINDB

Cooperating Units: None

Man Years:

Total:	.80
Professional:	.50
Other:	.30

Project Description:

Study data are being used to check published reports that the size of the placenta is increased by both mother-father (and thus mother-fetus) antigenic difference and by increasing sensitization of the mother against paternal antigens in repeat pregnancies. The question of fitness enhancement by larger placentas will be examined.

Extensive programming support from SSDP has been obtained and the availability of tabulations and analyses readily reportable in a publishable manuscript seems imminent. Preliminary computer outputs unsatisfactory in some details but reliable enough for general indications are quite consistent with the supposition that successive sensitization of gravidae (especially in low parities) to paternal antigens through placental implantation causes placental hypertrophy.

Serological investigations to check these results are to be proposed.

Honors and Awards: None

Publications: None

Serial No. NDB (CF)-68 PR/EG 1645
1. Perinatal Research Branch
2. Section on Epidemiology and Genetics
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Detailed Evaluation and Comparative Study of the Puerto Rican Cohort in the Collaborative Study

Previous Serial Number: None

Principal Investigators: Dr. Glen S. Bartlett, PRB, NINDB
Craig Humphrey, Department of Sociology, Brown University, Providence, Rhode Island

Other Investigator: Dr. N. C. Myrianthopoulos, PRB, NINDB

Cooperating Units: None

Man Years

Total:	.20
Professional:	.20
Other:	.00

Project Description:

This study is designed to investigate and define the characteristics of the Puerto Rican Cohort in three Collaborative Study Institutions, Columbia, New York Medical, and Pennsylvania hospitals, and to compare the cohort with the white and Negro cohorts at the same institutions. Emphasis is on socio-economic background, fertility, assimilation and acculturation, and the biological variables which seem to be influenced by these factors. The study is considering separately the mother, the infant, and the family into which the child is born. The present phase of the study is exploratory rather than hypothesis-testing, and is limited to the first year of the child's life.

The initial request for computer tabulations has been revised and resubmitted.

Honors and Awards: None

Publications: None

Serial No. NDB (CF)-68 PR/EG 1646
1. Perinatal Research Branch
2. Section on Epidemiology and Genetics
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Study of the Physical Growth of Children in the Collaborative Study

Previous Serial Number: None

Principal Investigator: Dr. Glen S. Bartlett, PRB, NINDB

Other Investigators: None

Cooperating Units: None

Man Years

Total:	.10
Professional:	.10
Other:	.00

Project Description:

This study is designed to develop growth curves on Collaborative Study children using two mathematical approaches. The first will take percentile and standard deviation distributions of measurements at various ages and plot growth curves. The second will evaluate the growth of the children individually using least squares linear regression, to develop growth rates at different points in time as well as growth curves from computed measurements. The two methods will be compared for comparability of the resulting curves.

The present phase of the study is aimed at population description and is limited to race and sex breakdowns; future phases will evaluate comparative growth of other subgroups of the population such as premature infants and infants with certain neurologic diseases. Curves are being developed on infants from birth through 7 years.

Requests for computer handling of the data have been submitted and are being processed.

Honors and Awards: None

Publications: None

Serial No. NDB (CF)-68 PR/EG 1647
1. Perinatal Research Branch
2. Section on Epidemiology and Genetics
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Development and Evaluation of an Index of Reproductive Performance for the Purpose of Identifying High Risk Pregnancy Suspects

Previous Serial Number: None

Principal Investigator: Dr. Glen S. Bartlett, PRB, NINDB

Other Investigators: None

Cooperating Units: None

Man Years

Total:	.05
Professional:	.05
Other:	.00

Project Description:

This study is designed to develop a mathematical index of reproductive performance based on prior pregnancy wastage -- fetal and infant mortality and morbidity -- for the purpose of identifying the so-called "high risk" pregnancy suspect. The predictive value of the index will be tested by applying it to future pregnancy performance (first and subsequent study pregnancies). The relationship of the index to socioeconomic parameters known to be related to poor reproductive performance will also be investigated.

A request for computer handling of the data is being prepared.

Honors and Awards: None

Publications: None

Serial No. NDB (CF)-68 PR/EG 1648
1. Perinatal Research Branch
2. Section on Epidemiology and Genetics
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Further Investigation of the Socioeconomic Index as a Descriptive and Predictive Instrument

Previous Serial Number: None

Principal Investigators: Dr. Glen S. Bartlett, PRB, NINDB
Dr. N. C. Myrianthopoulos, PRB, NINDB

Other Investigators: None

Cooperating Units: None

Man Years

Total:	.05
Professional:	.05
Other:	.00

Project Description:

The socioeconomic status score or socioeconomic index, developed by the Bureau of the Census for use with the 1960 Census, has been used with good results in this Section to describe the Collaborative Study population, and by others to describe other populations. This study is designed to explore mathematically the three component parts of the index -- education and occupation of the head of household, and family income -- in order to assess their relative contributions to the index; to evaluate the ability of the index to encompass other socioeconomic variables not used in deriving the index; and to investigate whether or not the index, in addition to being descriptive, can also be used as a reliable predictive instrument.

Linear discriminant function and multiple regression analysis will be used to determine appropriate weights to be applied to the component factors, and correlation coefficients will be obtained between the index and its components, and external variables. The present phase is based on information obtained when the gravida registered for her first study pregnancy; later phases will compare gravidae at subsequent study pregnancies and at the 7-year follow-up interview.

A request for computer handling of the data is being prepared.

Honors and Awards: None

Publications: None

Serial No. NDB (CF)-65 PR/P 1278
1. Perinatal Research Branch
2. Section on Pathology
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Biologic Pattern Data Processing

Previous Serial Number: Same

Principal Investigators: Lewis E. Lipkin, M. D.
Russell A. Kirsch

Other Investigators: None

Cooperating Units: Artificial Intelligence Group,
National Bureau of Standards

Man Years

Total: 6.5
Professional: 4.3
Others: 2.2

Project Description:

LISP Image Processing on the Q-32 Computer: During this period the Q-32 computer at Systems Development Corporation has become our main research tool. The availability of the LISP language with a powerful implementation and a very convenient editor has been a source of research convenience to us and also has given us the experience to help in the planning and design of other systems. Thus, the planning for the image processing facility at the Division of Computer Research and Technology at NIH has been largely influenced by the kind of image processing that we have been doing on the Q-32 in LISP. The LISP implementation on the Q-32 does not provide any special image processing facilities but rather general purpose list structure manipulation capabilities. Consequently, we added to this LISP system several functions using the assembler LAP to provide basic image processing capabilities at an efficiency greater than that provided by the LISP language. All of these functions are embedded in LISP and hence usable as ordinary LISP functions. Since a comparatively small number of programs have to be written to provide a complete system capable of rather wide generality for image processing, the investment in such programming is small compared to the returns which are obtained.

The basic programs written include:

a. A program for computing arbitrary Boolean functions of two binary image planes.

b. A program for computing an arbitrary Boolean function of every point in a single binary plane expressed as a function of arbitrary neighbors of that point.

c. A function for counting neighborhood points of each point in a plane and thresholding the resultant counts.

d. A program for shifting a plane by a specified x and y.

e. A program for isolating an arbitrary set of connected points in a plane, hence for selecting out continuous connected objects or blobs.

Using the basic functions, high level functions were written in LISP that enabled us to get density histograms of discrete objects in pictures, programs that enabled us to experiment with various types of binary threshold operations on the multiple level pictures, and programs to select arbitrary sections of images for printing display on the Teletype printer. These programs were used in conjunction with inputs on magnetic tape that contained complete scans for a piece of cortex tissue. The programming language and some programs in that language will be described in a forthcoming report that will enable other users of the Q-32 to experiment with these programs.

There were also some other image processing experiments on Q-32. One was a small attempt to solve the picture syntactic analysis or parsing problem by reducing pictures to a one-dimensional counterpart. These strings were subject to a kind of syntactical analysis. Another effort was devoted to display problem to enable simple geometric shapes representing articular parts of images (especially nerve cells) to be displayed in such a way that the proper topological relations held, notwithstanding the fact that the various objects subject to these relations had different shapes. This type of program has some applicability in the synthesis of images for graphical display.

List Structure Manipulation for Image Descriptions: A set of programs were developed (also in the LISP language) which enabled the description of the articular structure of nervous system tissue to be manipulated. These list structures were obtained from Dr. Lipkin. They describe the organization of CNS tissue from the gross morphological level all the way down to the level at which single cells are described in terms of their component structures. The programs written enable searching of these list structures to find such things as the structures which contain a given one or the contents of a given structure. Attempts were thus made to describe

in complete algorithmic form the relations that hold in nervous system tissue structure between objects and their parts, and between objects and their contents, and relations which are of a taxonomic nature among objects in tissue. Since this description manipulation is within the same language as the image processing programs which the descriptions purportedly pertain to, it was possible to connect the two kinds of programs together in such a way that one could find for a structure of a given name like a cell body, not merely the names of the components of a cell body but also the pictures obtained from a suitable picture processing program of the contents of that cell.

1108 Univac LISP Interpreter: Since there was no LISP available locally at NBS, a small interpreter was written for the 1108 Univac to enable LISP programs to be run. This interpreter is presently not complete, although most programs not involving numerical computations can be run.

Microscope Scanner - PDP-8 Hook-Up Design: Plans are in the final stages for the connection of a galvanometer scanner for the LINC - PDP-8 computer in Dr. Lipkin's laboratory. Preliminary investigation of the scanner and suitability of connecting it to the machine has been completed as well as has some design on the actual interconnection hardware. This scanner which is owned by the National Cancer Institute is on loan to Dr. Lipkin. During the coming fiscal year, this will provide a major tool in scanning images directly through the microscope with programmable light sources as well as microscope and stage control. Since the images to be produced will be available in magnetic tape form, all the image processing capabilities developed on the Q-32 computer can be devoted to the processing of these microscope images to be obtained in Dr. Lipkin's laboratory.

Rotating Drum Scanner: Dr. George Moore completed the documentation of the construction of and use of the rotating drum scanner for photographs that was built at NBS. This report, No. 9429 "Practical Scanner Unit for Precision Analysis of Micrographs," makes it possible for others to duplicate the comparatively inexpensive scanner that Dr. Moore built which was a copy of the scanner used for preparing our original data.

Spectrophotometer Connection: Hardware was designed and constructed for the connection of Dr. Lipkin's microspectrophotometer with controlled monochromator light source to the LINC - PDP-8 computer. When this connection is complete the microspectrophotometer will be under the complete control of the computer with direct readings obtainable through analog to digital conversion hardware in the computer.

Seminar on Computer and Computation Theory: A significant part of our efforts has been of an educational and communication nature during the present period. A Seminar on Computer and Computation Theory was conducted. One of its main accomplishments was to enable some 24-48 participants (largely from NIH) to develop an understanding of the contemporary theory of both machines and the process of computation.

During this period many guests formally and informally participated in our program, in some cases through the use of the remote computer communication facility from locations elsewhere than the Washington area. The Image Processing Group at DCRT also made extensive use of our Q-32 experience both for image processing research of their own as well as for the design of their image processing facility.

Meeting of PAX Picture Processing Language Users: A meeting was also held in May 1967 for the community of users of the PAX picture processing language which was installed by us on the M.I.T. MAC computer. From this meeting evolved a reasonable consensus of how to extend image processing techniques into the multiple tone image kind of problems which are of primary biological interest.

Honors and Awards: None

Publications:

Author: Moore, George A.: A Practical Scanner Unit for Precision Analysis of Micrographs. U.S. Dept. of Commerce, National Bureau of Standards Report 9429. Washington, D.C., 1967, 97 pp.

Serial No. NDB (CF)-66 PR/P 1342
1. Perinatal Research Branch
2. Section on Pathology
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: The Length of the Umbilical Cord

Previous Serial Number: Same

Principal Investigators: Toshio Fujikura, M. D.
Luz A. Froehlich, M. D.
Lewis E. Lipkin, M. D.

Other Investigators: None

Cooperating Units: All Collaborative Institutions

Man Years

Total: .04
Professional: .04
Others: .00

Project Description:

Objectives: To determine if there is a relative correspondence between cord length and the two main indices of embryonic growth, namely birthweight and gestational age.

Methods Employed: The cohorts in the study were single birth core cases where the total length of the umbilical cord was available in the PED-1 form (Examination of the Neonate). Only infants with birthweights of 1,001 grams and over and gestational ages of 28 to 43 weeks were included. For birthweight - cord length associations, a total of 8,696 whites and 9,290 Negroes were available for analysis and for gestational age - cord length relationships, 4,869 whites and 6,434 Negroes were analyzed.

Major Findings: Mean cord lengths showed a progressive increase in both white and Negro with increments of gestational age and birthweight. Percentage distribution on cord lengths also showed a gradual shift from the shorter to the longer cord with increasing gestation and birthweight.

The mean cord length in the Negro was usually less than its white counterpart, the difference being constant at about 1.4 cm at each gestation interval.

Significance to Bio-medical Research and the Program of the Institute: There is a paucity of comprehensive studies on the length of the umbilical cord. In two separate studies, it has been claimed that there is very little correspondence between cord length and fetal weights and there is no evidence of growth in cord length after the 28th week of gestation. These hypotheses were not supported by the results of the present study where cord lengths on a much larger study group were analyzed.

Proposed Course: Because of the availability of total cord lengths in a vast number of cases, the study of the length of the umbilical cord and its associations with a multiplicity of factors using collaborative study data lends itself to wide exploration. It is contemplated that this study be enlarged to include analysis of its associations with other indices of growth such as crown-rump length, crown-heel length, placental weight, as well as other placental findings such as type of cord insertion, placental shape, etc. In addition, possible effects on cord length of selected conditions such as single umbilical artery, true knots of cord, cord entanglement, cardiovascular and other malformations, anemia in pregnancy, diabetes mellitus, dysmaturity, etc., will be investigated.

Honors and Awards: None

Publications: None

Serial No. NDB (CF)-66 PR/P 1345
1. Perinatal Research Branch
2. Section on Pathology
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Influencing Factors in Sudden Unexpected Death

Previous Serial Number: Same

Principal Investigators: Toshio Fujikura, M. D.
Joseph Drage, M. D.

Other Investigators: Luz A. Froehlich, M. D.

Cooperating Units: All Collaborative Institutions

Man Years

Total: .10
Professional: .08
Others: .02

Project Description:

Objectives: Sudden unexpected death in infancy presents a serious unsolved problem. It accounts for over 10% of infant mortality in the United States and 20% in England. In the majority of cases, the pathologic findings are minimal. Previous exhaustive studies have concentrated on the neonatal and postnatal conditions. The purpose of this study is to investigate all possible influencing factors on sudden death, especially prenatal and maternal problems which have not been explored in previous studies. Two hundred and seven cases of sudden unexpected deaths in the collaborative study material were identified. The possible influence of the following factors will be investigated: sex, race, birthweight, gestation, placental weight, placental infection, autopsy findings, maternal diseases, type of feeding, Apgar score and socio-economical factors.

Methods Employed: Sudden death cases were divided according to the following:

a. Sudden Unexplainable Death (SUD). Autopsy findings were minimal and could not adequately explain death. 96 cases.

b. Sudden Explainable Death (SED). Death was sudden but autopsy findings were adequate to explain death. 37 cases.

c. Mixed Sudden Death (MSD). Consisted of non-autopsied cases or known autopsied cases where protocol had not yet been received at PRB. 68 cases.

The proportion of SUD to SED cases was obtained in the white and the Negro, and the MSD cases were divided and added onto the corresponding groups using this proportion.

Major Findings: (1) SUD cases were largely premature, not so much in birthweight (white 18.2%, Negro 25.8%) as in gestational age (white 31.0%, Negro 43.9%). Percentage of placentas weighing less than 400 grams was also higher in the SUD group in both white and Negro compared to controls (single live births or SLB). (2) Majority of SUD's occurred between 1-4 months of age and very rarely after six months. (3) Most of the SUD's occurred in the winter months. (4) The peak of SUD cases occurred in somewhat lower socio-economic strata compared to the general collaborative study population in both white and Negro. (5) Pediatric factors (Apgar score, type of feeding, etc.) and obstetric factors (maternal diseases during pregnancy) are in process. (6) Estimated incidence:

SUD (Sudden Unexplainable Death)

White 2.1 per 1,000 births (25,071 births)
Negro 3.3 per 1,000 births (24,786 births)
White 39.7 per 100 infant and child deaths (136 deaths)
Negro 34.3 per 100 infant and child deaths (242 deaths)

SED (Sudden Explainable Death)

White 0.7 per 1,000 births
Negro 1.2 per 1,000 births
White 14.7 per 100 infant and child deaths
Negro 12.4 per 100 infant and child deaths

Proposed Course: The pathology portion of the study on sudden unexpected death is completed. The evaluation of clinical data by the Section on Pediatric Neurology is still in progress.

Honors and Awards: None

Publications: None

Serial No. NDB (CF)-66 PR/P 1351
1. Perinatal Research Branch
2. Section on Pathology
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Placental Changes After Experimental Abruptio and Fetal Vessel Ligation of Rhesus Monkey
(Formerly - Fetal Vessel Ligation in Rhesus Monkey Placentas)

Previous Serial Number: Same

Principal Investigators: Ronald Myers, M. D.
Toshio Fujikura, M. D.

Other Investigators: None

Cooperating Units: Perinatal Physiology Laboratory, NINDB
San Juan, Puerto Rico

Man Years (Indicates Man Years used only by workers in Bethesda and does not include years used by workers in Puerto Rico.)

Total: .08
Professional: .06
Others: .02

Project Description:

Objectives: To produce and analyze pathologic lesions in the Rhesus monkey placenta following experimental abruptio and closure of the fetal placental circulation.

Methods Employed: The pregnant monkeys (Macaca mulatta) used in this study were obtained from a caged breeding colony at the Laboratory of Perinatal Physiology in San Juan, Puerto Rico. Timed mating and animal care have been described in previous papers. Thirteen monkeys underwent fetal placental vessel ligation and six monkeys experimental abruptio placentae. Both procedures were done at 100-120 days' gestational age. The animals were later delivered by cesarean section at 156-158 days' gestational age unless the pregnancies had already terminated by spontaneous vaginal delivery. The placentas were examined grossly and microscopically. Placental outline was determined by transillumination through the uterine wall or by palpation. The placental edge was approached by incision without rupture of the amniotic sac. Extra amniotic ligation of fetal

vessels coursing the fetal surface of the placenta was performed. Arteries and veins running alongside each other were ligated together by silk thread. The vessles ligated were either those near the insertion of the umbilical cord or those bridging the two placental lobes. Experimental abruptio placentae was accomplished by simple manual separation of the placenta from the uterine wall. Manual separation was restricted to the entire accessory lobe in which there was no insertion of the umbilical cord.

Major Findings: After vascular ligation of fetal vessels using Rhesus monkey placentas at 100-120 days' gestational age, syncytial trophoblast and cytotrophoblast was found to be abnormally increased 40-50 days after treatment. No intervillous thrombi nor increased fibrin deposits were noted in the devascularized lesions. This suggests that intervillous thrombosis and fibrin deposition do not result as long as the maternal circulation is intact. The monkey fetuses appear to tolerate vascular ligation of the placenta (8 live births in 13 monkeys) but not experimental abruptio placentae (all 6 were stillbirths). As in human abruptio placentae, derangements in the maternal circulation provoked fetal death in utero in these animals.

Honors and Awards: None

Publications:

Myers, R., and Fujikura, T.: Placental changes after experimental abruptio and fetal vessel ligation of Rhesus monkey. Amer J Obstet Gynec, 100:6, pp. 846-851, March 15, 1968.

Serial No. NDB (CF)-66 PR/P 1352
1. Perinatal Research Branch
2. Section on Pathology
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: The Neuropathological Study of a Series of Selected Monkey Brains from Animals in the Perinatal Period

Previous Serial Number: Same

Principal Investigator: Jack H. Carleton, M. D.

Other Investigators: Lewis E. Lipkin, M. D.

Cooperating Units: Bionetics Research Laboratory, Inc.

Man Years

Total: .10
Professional: .05
Others: .05

Project Description:

Objectives: This study was initiated to evaluate as a comparison to the Perinatal Research Project material the brains of the primate perinatal period according to the protocol established for the processing of whole brains coming from the collaborative study. Data on the prenatal period, delivery, neonatal care, developmental aspects, and circumstances of death in these cases has been collected and will be considered after the neuropathological findings have been described.

Methods Employed: The specimens for study have been processed according to project methods including whole and sectioned brain photography, and project staining procedures. A microscopic examination protocol is being devised so that all brains can be compared in tabular form.

Major Findings: All 103 brains in the series have been processed and classified as to age, species and quality of histological preparation. Ages range from stillbirth to 2½ years for the three major species which will be evaluated. The detailed protocol for describing the neuropathological observations has not been completed since our major effort has been to process all project specimens to the paraffin embedded stage and then proceed with histological evaluations. It is anticipated that during the

next year the protocol for description of these brains in comparison with the project material will be completed and preliminary reports of the microscopic findings in these perinatal monkeys will be completed.

Significance to Bio-medical Research and the Program of the Institute: It is anticipated that this study will enhance our understanding of perinatal neuropathology and serve as a laboratory control for evaluation of technical procedures used in the project's protocol.

Proposed Course: Continue to completion as outlined.

Honors and Awards: None

Publications: None

Serial No. NDB (CF)-66 PR/P 1353
1. Perinatal Research Branch
2. Section on Pathology
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: A Sequential Study of Ultrastructural Changes in an Experimentally Produced, Traumatic Brain Lesion

Previous Serial Number: Same

Principal Investigator: Jack H. Carleton, M. D.

Other Investigators: John L. Priester

Cooperating Units: None

Man Years

Total: .4
Professional: .2
Others: .2

Project Description:

Objectives: To describe in detail the sequential ultrastructural changes occurring as a response to a reproducible wound in the mouse brain.

Methods Employed: Same as in previous reports. In addition, special stains and light optical systems have been applied to the evaluation of the lesions.

Major Findings: This project has been divided into eight separate phases. Six of these phases have been completed and the seventh "Large Epoxy Tissue Section of Mouse Brain" was prolonged while the development of specific technical procedures was undertaken. Phase seven was completed and a demonstration showing the application of large epoxy sections to central nervous system investigations was prepared and shown as part of a general exhibit at three separate meetings.

Significance to Bio-medical Research and the Program of the Institute: This investigation has been undertaken to apply improved electron microscopic techniques in an effort to enhance and clarify existing knowledge pertaining to the response of the brain to trauma.

Proposed Course: The completion of the eighth stage of this project was postponed but now is nearing completion. A paper describing the results is being prepared. If time and facilities permit, the effects of diet, hyperoxygenation, anoxia, infection and immune response will be evaluated.

Honors and Awards: None

Publications: None

Serial No. NDB (CF)-66 PR/P 1354
1. Perinatal Research Branch
2. Section on Pathology
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Automated Microspectrophotometry Employing the LINC Computer

Previous Serial Number: Same

Principal Investigator: Lewis E. Lipkin, M. D.

Other Investigators: None

Cooperating Units: Biomedical Engineering and Instrumentation Branch, DRS

Man Years

Total: 1.5
Professional: .5
Others: 1.0

Project Description:

Microspectrophotometry of neural tissue sections is extremely difficult, time consuming, subject to serious instrumental errors and requires extensive computations (e.g., as in two wave length methods) to obtain meaningful results. In each aspect of the foregoing, the use of a computer as a control and analytic device is of very great assistance indeed.

The objective of this study is threefold:

1. To demonstrate the use of a small general purpose computer in morphology (analogous to its already demonstrated values in neurophysiology).

2. To investigate the dynamics, quantifiability and reproducibility of Gallocyanin staining of CNS tissues.

3. To serve as an experimental programmable scanner to be interfaced with a large software system, LISP-PAX, as developed by Individual Project NDB (CF)-65 PR/P 1278.

In October of 1967, a LINC-8 computer was delivered to this laboratory. Acceptance testing was completed by the end of November. The next three months were occupied in systems programming, an investment of time designed to take advantage of the greatly increased core memory of the LINC-8 over the classic LINC. In consultation with engineers at NBS, it was decided to run the stepping motors via the interrupt system (in order to increase their speed) and therefore, the interface was partially reconstructed. Improvements have also been made to the optical detection system.

The completion of the revisions should take place during the first half of fiscal year 1969 under the direction of an electrical engineer, who will take full technical (as opposed to biological) responsibility for the system.

The Perkin Elmer scanner, designed for NCI, and now on loan to this section, will also be interfaced to this system and will thus permit digitized as well as two wave length modes of quantitation. Design specifications for this interface have been drawn up and will be implemented during the next fiscal year.

Proposed Course: Beginning with the next reporting period it is proposed that this project be merged, at least for reporting purposes, with the biological image processing project for which, from a research viewpoint, it will be integrated. The system will function during the second shift as originally intended, i.e., as a production microspectrophotometer. The operations of this system are described in last year's report.

Honors and Awards: None

Publications: None

Serial No. NDB (CF)-66 PR/P 1355
1. Perinatal Research Branch
2. Section on Pathology
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Factors Influencing Quantitative DNA Staining

Previous Serial Number: Same

Principal Investigator: Jack H. Carleton, M. D.

Other Investigators: Charles Spencer, M. D.
Lewis E. Lipkin, M. D.

Cooperating Units: Mortimer Mendelson, M. D.
Department of Radiology
University of Pennsylvania

Man Years

Total: .4
Professional: .3
Others: .1

Project Description:

Objectives: To devise ways of testing and to determine the degree of influence that various factors have on the microspectrophotometric measurements of DNA staining. Factors which are under investigation include stain fading, species and embryological development differences in absorption curve characteristics, and staining progressivity.

Methods Employed: Instrumentation and procedures used in this project have been developed under the direction of the investigators and include a specially constructed two wave length cytophotometer and a microscopic slide perfusion chamber. In addition, photographic methods have been employed to compare stain progressivity and evaluation of pictorial information has been conducted on a Zeiss Integrating Densitometer at the AFIP.

Major Findings: The investigation of Gallocyanin progressivity in whole cells using the cell perfusion chamber developed in 1966 has been continued and the photographic phase using the Zeiss Integrating Densitometer at the AFIP has been completed showing for the first time progressivity curves for individual cells. The development of a vacuum system to

maintain flow of stains and easy solution changing along with the use of epoxy sealing for the chamber has permitted the use of Gallocyanin DNA-RNA staining over a period of six days.

Significance to Bio-medical Research and the Program of the Institute: Greater understanding and documentation of the factors influencing quantitative DNA staining is mandatory if these methods are to become more useful tools in the microscopist's search to automate and quantitate the evaluation of the images. It is to this aim that this project is directed both for use within the section's investigations of automated biological image processing and for this field of research in general.

Proposed Course: The evaluation of actual stain progressivity as measured directly on a microspectrophotometer has been postponed until the instrumentation becomes available. It is anticipated that this phase of the project will be started during the 1968-1969 period as well as a more sophisticated evaluation of the photographic films showing progressivity for both Feulgen and Gallocyanin.

Honors and Awards: None

Publications: None

Serial No. NDB (CF)-67 PR/P 1517
1. Perinatal Research Branch
2. Section on Pathology
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Diagnosis of Sickling by Placental Examination - Geographic Differences in Incidence

Previous Serial Number: Same

Principal Investigators: Toshio Fujikura, M. D.
Luz A. Froehlich, M. D.

Other Investigators: None

Cooperating Units: 7 Collaborative Institutions

Man Years

Total: .16
Professional: .12
Others: .04

Project Description:

Objectives: To determine the incidence of maternal sickling in the collaborative study Negro population according to geographic distribution, by a retrospective study of consecutive placental slides on Negroes.

Major Findings: When the placenta separates from the uterine wall the resulting hypoxia creates a natural sickling preparation of the trapped erythrocytes in the placenta. A histologic examination of 2,117 consecutive placentas of Negro women enrolled in the collaborative study showed a sickling incidence of 9.4%. Sickling rates in the southern institutions (11.0% - 12.2%) were higher than in the northern institutions (6.1% - 8.4%). It is postulated that these geographic differences in sickling rates may indicate increased admixture of Caucasian blood among northern Negroes. Permanent histologic sections of the placenta offer the advantages of retrospective study, uniformity of technique and reconfirmation of diagnosis, which are not possible with sickle-cell preparations on peripheral blood.

Proposed Course: Although sickle cell anemia (only 1 in 40 sickle cell trait cases or .2%) in pregnant Negroes has been studied, studies on the sickle cell trait which seems to be a very common condition among pregnant Negro women has been completely neglected.

A preliminary review of 596 project Negro women who have sickling in peripheral blood shows 13 or 2.2% infant deaths. This rate is significantly higher than .8% in the overall Negro project population. However, perinatal death rates of the reviewed cases are within the normal range. An investigation is underway to compare sicklers with non-sicklers in regard to selected variables such as selected maternal diseases, parity and maternal age, previous fetal loss, menarche, birthweight and gestational age.

Honors and Awards: None

Publications:

Fujikura, T., and Froehlich, L.A.: Diagnosis of sickling by placental examination - geographic differences in incidence. Amer J Obstet Gynec, 100:8, pp. 1122-1124, April 15, 1968.

Serial No. NDB (CF)-67 PR/P 1518
1. Perinatal Research Branch
2. Section on Pathology
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Preparations of Large Epoxy Sections for Light and Subsequent Electron Microscopy

Previous Serial Number: Same

Principal Investigators: Jack H. Carleton, M. D.
John L. Priester

Other Investigators: Phillip M. Grimley, M. D.
Herman J. Michelitch

Cooperating Units: Pathologic Anatomy Branch, NCI

Man Years

Total: .8
Professional: .4
Others: .4

Project Description:

Objectives: To develop methods of embedding, sectioning and staining large specimens which will enable the same area to be examined by both light and electron optics, thus eliminating the differences between conventional histopathology and ultrastructural interpretations.

Methods Employed: The establishment of this technique and apparatus for the preparation of large epoxy sections included the modification of existing methods and the development of new procedures in the following areas:

a. Embedding procedures for a variety of epoxy resins useful for one to ten micron thick sections.

b. Determination of best microtomes and ultramicrotomy methods for preparing 2x2 cm sections.

c. Specially constructed apparatus for re-embedding and viewing of sections for ultramicrotomy.

d. Staining methods useful for large epoxy sections.

e. Trial of techniques on all types of tissues.

Major Findings: This project has established complete methods of embedding, sectioning, staining, precision re-embedding and final ultramicrotomy, thus enabling investigators to study ultrastructural changes by examination of identical areas either with light or electron microscopes. This complete correlation of low and ultra high magnification observations bridges the chasm between conventional histopathology and ultrastructural interpretation. The investigation has produced a final microlocator-polymerization device which is now being manufactured by the Nikon Company. A technique's pamphlet has been prepared and distributed at three scientific meetings where a demonstration of the entire method has been presented. In addition to their primary use in electron microscopy these large epoxy sections afford excellent material for light optical study in the following ways:

a. Clarity of detail is improved both by the osmium fixation and the reduced shrinkage-distortion of membranes during plastic embedding.

b. Thin sections of very soft and brittle tissue elements may be obtained with minimal artifactual disruption.

c. Optimal light resolution permits identification of otherwise obscure structures and subcellular particles.

d. Differential staining of epoxy sections yields information concerning the distribution of cell types.

e. The osmium treatment provides a simultaneous lipid stain which may be enhanced by paraphenylendiamine.

f. Small surgical biopsies may be embedded entirely in large plastic blocks for complementary light and electron microscopic investigation making arbitrary subdivisions of small samples unnecessary.

During the past year improvements in technique have been completed and consist of the following:

a. The application of Nomarski interference contrast equipment for transmitted light for the viewing of stained and unstained sections has greatly improved resolution and ease of interpreting light microscopic large plastic sections prior to re-embedding.

b. A newly designed embedding tray has greatly facilitated the embedding procedure.

c. The design and use of teflon cover slip weights has improved tissue flatness for both re-embedding section preparation and in permanent section mounting.

d. The technique of Gallocyanin staining has been improved and now awaits quantitative evaluation with the microspectrophotometer.

e. New embedding media have been utilized for the embedding of tissue and although histochemical staining must be now evaluated, they give good cell preservation. These media included glycol methacrylate, 2-hydroxypropyl methacrylate, durcupan and methacrylate glycol distearate.

Significance to Bio-medical Research and the Program of the Institute: This two-stage embedding procedure enables the overall investment of professional time to be significantly reduced since ultrastructural investigations can be confined to a few carefully selected histological samples. The sample finally examined by electron microscopy is only about 1/100 of the depth inspected visually and thus it is possible to span a wide range of magnifications within a limited field. Photographic correlations of single cells, cell inclusions or localized lesions can now be easily made by all investigators who previously were hampered by tissue sampling techniques and precise neuroanatomical location of ultrastructure. In addition, the extent and distribution of lesions need no longer be a tedious and sometimes futile search.

Proposed Course: The methods derived from this project permit the application of electron microscopy to a number of specific perinatal research problems which are continuing in our laboratory. The detailed study of Gallocyanin staining specificity and its quantitation will be continued. In addition, histochemical staining of the new water soluble embedding media will be evaluated.

Honors and Awards: None

Publications:

Grimley, P.M., Carleton, J.H., Michelitch, H.J., and Priester, J.L.: Techniques of preparing large plastic sections for conjugate light and electron microscopy. J Cell Biol, 31: 130A, November 1966.

Serial No. NDB (CF)-67 PR?P 1519
1. Perinatal Research Branch
2. Section on Pathology
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: The Study of Unilateral Thickening of Fetal Arteries on the Placenta

Previous Serial Number: Same

Principal Investigators: Toshio Fujikura, M. D.
Jack H. Carleton, M. D.

Other Investigators: None

Cooperating Units: All Collaborative Institutions
Suburban Hospital, Bethesda, Maryland

Man Years

Total: .10
Professional: .05
Others: .05

Project Description:

Objectives: To describe and evaluate a unilateral thickening of the walls of fetal arteries on the placenta, and to investigate the relationship of this peculiarity to structures found in umbilical cords, gestational age, anatomical distributions and arteriosclerosis.

Methods Employed: This study consisted of the histological evaluation of arteries in 11 fresh human placentas collected from the delivery room of Suburban Hospital, Bethesda, Maryland and 202 consecutive term placentas plus 96 abortion placentas from the Perinatal Research Project cases. The fresh placentas were processed by a variety of methods to provide as much technical information as possible.

Major Findings: The unilateral muscular thickening was found to have its onset at 12 weeks gestation increasing in frequency with increments of gestational age and later being associated with intimal thickening in the term placenta. Of the 202 consecutive term placentas, 84.1% or 170 showed this peculiar thickening of the "lower" arterial wall. In contrast to atherosclerosis, the medial muscular growth was more pronounced than the intimal thickening and there was no remarkable lipid deposition.

Significance to Bio-medical Research and the Program of the Institute: This study provides a beginning of an attempt to explore the histological variations existing in the developmental stage of the human extra-embryonic vascular system. Very little information is available on this subject and the relationships of various peculiarities to subsequent lesions in diseased conditions of either the fetus or mother. This finding of a localized arterial thickening resembling early arteriosclerosis may provide an excellent model for the study of atherosclerosis and its etiology in the human under a variety of conditions.

Proposed Course: The initial aspect of the study was completed in 1966-1967 and published in the American Journal of Obstetrics and Gynecology. Only preliminary ultrastructural investigation of this thickening has been undertaken and it is anticipated that in 1967-1968 twelve additional fresh placentas will be perfused and a detailed description of their ultrastructure will be completed and published.

Honors and Awards: None

Publications:

Fujikura, T., and Carleton, J.: Unilateral thickening of fetal arteries on the placenta resembling arteriosclerosis. Amer J Obstet Gynec, 100:6, pp. 843-845, March 15, 1968.

Serial No. NDB (CF)-68 PR/P 1649
1. Perinatal Research Branch
2. Section on Pathology
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Congenital Malformations in Perinatal, Infant and Child Deaths

Previous Serial Number: None

Principal Investigators: Luz A. Froehlich, M. D.
Toshio Fujikura, M. D.

Other Investigators: None

Cooperating Units: All Collaborative Institutions

Man Years

Total: 1.2
Professional: .8
Others: .4

Project Description:

Objectives: To report the analysis of malformations on autopsied stillbirths, neonatal, infant and child deaths in the collaborative study and to determine the underlying relationship of multiple and single malformations to sex, race, type of death, birthweight, gestational age, and maternal age.

Methods Employed: This report was based on 43,127 consecutive single births delivered of randomly selected collaborative study registrants from January 1, 1959 to December 31, 1964. Abortions were not included. The present study was limited to autopsied deaths of collaborative project cases of which there were 1,626. The autopsy protocols were carefully hand reviewed for malformations.

Malformations were classified into two groups. Group A malformations included all uniformly reported microscopic abnormalities of structure present at birth and resulting from faulty embryological development (based on definition by McKeown and Record) which normally would have been completed by the end of the ninth week. Group B included anomalies which were thought to be a secondary effect of Group A malformations or were felt not to be universally accepted as malformations, or where uncertainty as to consistency of reporting existed in autopsied material. Excluded from

either group were inborn errors of metabolism, hereditary blood or neurological diseases, microscopic abnormalities, congenital tumors and leukemia. Multiple malformations were defined as Group A malformations involving two or more organ systems. Single malformations were those involving only one organ system, regardless of the number of malformations within the system. Overall, single and multiple malformation rates were based only on Group A malformations and were calculated using number of deaths as denominator. All attempts were made not to overcount and therefore the resulting figures were conservative.

Major Findings: A review of 1,626 autopsied stillbirth, neonatal and infant and child deaths out of a total of 43,127 single births in the collaborative study was undertaken in which 259 or 15.9% had unequivocal (Group A) congenital malformations. Malformation rates for each type of death and sex were consistently higher in whites than in Negroes. In either race there was no significant difference in overall malformation rates between males and females. However, multiple malformations were most frequent in white females, especially in stillbirths, than in white males or in Negroes of either sex. In both whites and Negroes, although the malformation rates were higher in females among stillbirths and infant and child deaths, the malformation rates were remarkably higher in male neonatal deaths, mostly due to a preponderance of single malformations in the latter. All but one of the multiply malformed cases and 61.9% of those with single malformations had at least one lethal malformation indicating that differences in malformation rates were largely influenced by lethal malformations. Malformation rates increased stepwise with increments of gestational age, the highest rates being consistently those in the 38 weeks or more gestational age group. Higher incidences in the lower birthweight intervals were noted in white males with multiple malformations and in all malformed white females, suggesting the possibility of runting in these groups. That malformation rates were highest in the highest gestational age interval suggests that malformations are of greater significance in the mature than in the premature baby that dies, and also that the presence of malformations in viable fetuses does not necessarily result in early intrauterine death or premature expulsion from the uterus.

In the single live births the mean maternal age in Negroes was lower than in whites. But for most selected malformations the mean maternal age in Negroes was equal to or higher than in whites. This suggests that the optimum ages for many malformations are past the peak of reproductivity in the Negro and may have an influence on the generally lower incidence of malformations in Negroes. Mothers of multiply malformed cases were not older than those with single malformations. The incidence of malformations was not significantly higher in the extremes of maternal age except in white females where the high rate in those 19 years old or less was mainly due to multiple malformations (22.0%).

Anencephaly was particularly common among white females and their mothers were usually young. Atresia of the ureter or urethra was more common in males, particularly in Negroes. In males of both races involvement of the cardiovascular system was frequently limited to this system in contrast to females. Transposition of great vessels was more frequent in males.

The cardiovascular system was the system most often involved by malformations in both sexes and races. Second in rank was the central nervous system in white females and the genito-urinary system in Negroes of both sexes.

Paradoxically the malformations associated with Mongolism, a chromosome abnormality, were clustered around the 6-8 week critical period of development. However, those associated with other selected malformations were fairly diffusely scattered across the entire spectrum of critical period of development.

This paper was read at the Second International Workshop in Teratology at Kyoto, Japan in April 1968.

Honors and Awards: None

Publications: None

Serial No. NDB (CF)-68 PR/P 1650
1. Perinatal Research Branch
2. Section on Pathology
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Placentation in Relation to Zygosity of Twins

Previous Serial Number: None

Principal Investigators: Toshio Fujikura, M. D.
Luz A. Froehlich, M. D.
Ntinos Myrianthopoulos, Ph. D.

Other Investigators: None

Cooperating Units: All Collaborative Institutions

Man Years

Total: .03
Professional: .02
Others: .01

Project Description:

Objectives: To analyze twin placentation in relation to zygosity, infant mortality, birthweight, gestational age and sex.

Methods Employed: This study was based on the placentas of approximately 600 twin sets in the collaborative study, excluding abortions. The placental gross and microscopic descriptions were double-checked by reviewing available twin placenta photographs and microscopic slides of the placenta and dividing membranes. The type of zygosity of each twin set, based on more than 25 blood antigens, was obtained from the Section on Epidemiology and Genetics.

Proposed Course: Twin placenta studies made by other investigators have either merely estimated the expected zygosity using Weinberg's differential method or have established zygosity on the basis of an insufficient number of blood antigens. This study purports to attain the aforementioned objectives and to improve on past twin placenta studies.

Honors and Awards: None

Publications: None

Serial No. NDB (CF)-68 PR/P 1651
1. Perinatal Research Branch
2. Section on Pathology
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: The Ultrastructural Evaluation of Developing Hyaline Membranes in Strain A Mice

Previous Serial Number: None

Principal Investigators: Toshio Fujikura, M. D.
Jack H. Carleton, M. D.

Other Investigators: John L. Priester

Cooperating Units: None

Man Years

Total: .3
Professional: .1
Others: .2

Project Description:

Objectives: To determine the pathogenesis of hyaline membranes produced by oxygen poisoning.

Methods Employed: Sequences of seven strain A mice (six weeks of age) were placed in a specially constructed positive pressure high oxygen cage and one animal removed every 24 hours. The animals were killed and the lungs removed, fixed and processed by the large epoxy section technique. Light and electron microscopic comparisons were then studied.

Major Findings: Comparisons of the light microscopy and ultrastructural changes occurring during oxygen poisoning are in progress; no conclusions can yet be drawn.

Significance to Bio-medical Research and the Program of the Institute: It is hoped that this project will shed some light on the origin and nature of the pulmonary hyaline membranes. Hyaline membrane disease in the postnatal period is being evaluated by PRB and may be correlated with this project.

Proposed Course: The evaluation will continue as outlined and additional animals used as needed.

Honors and Awards: None

Publications: None

Serial No. NDB (CF)-68 PR/P 1652
1. Perinatal Research Branch
2. Section on Pathology
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Ultrastructural and Histochemical Evaluation of the CNS in Mice Progeny when a Protein-Deficient Diet was Administered During the Second Half of Gestation

Previous Serial Number: None

Principal Investigators: Jack H. Carleton, M. D.
John A. Churchill, M. D.

Other Investigators: John L. Priester

Cooperating Units: Dr. Carl T. Hansen, Head,
Genetics Unit, Lab Aid Branch, DRS

Man Years

Total: .4
Professional: .2
Others: .2

Project Description:

Objectives: To elucidate any new anatomical changes induced in the brain by prenatal nutritional states and correlate these findings with reduced learning potential.

Methods Employed: Twenty female, black, C57, inbred mice were selected after their first normal pregnancy and mated in groups of three to one male. The beginning of fertilization was determined by the presence of a vaginal plug and no subsequent plugs. The three females in each group were then divided into three categories which consisted of high protein (55%), normal protein (26%), and no protein diets of equal calorie and supplement values. This diet was started on the tenth day of gestation and regular diet replaced when the mice were born. Some newborns were killed from each group, fixed in gluteraldehyde and embedded for large epoxy sections. At 21 days the mice were weaned. At two months of age all mice were tested at Hazleton Lab by a one-way discriminating avoidance test. The animals were then perfused with gluteraldehyde or formalin and processed for electron microscopy or microspectrophotometry.

Major Findings: The comparison of ultrastructure, Feulgen DNA, and Gallocyanin chrome alum DNA-RNA has not been completed but will be evaluated and compared to testing results during the next fiscal year.

Significance to Bio-medical Research and the Program of the Institute: This investigation was derived to test the hypothesis and trend found in the PRB-collaborative data that there is a relationship between proteins, intelligence and mental retardation. The project may produce the information necessary to permit a better evaluation of the absence or presence of submicroscopic lesions from intrauterine nutritional impoverishment.

Proposed Course: The material collected will be studied by the outlined methods and reported. Continuation of the project will depend on the outcome of this evaluation.

Honors and Awards: None

Publications: None

Serial No. NDB (CF)-68 PR/P 1653
1. Perinatal Research Branch
2. Section on Pathology
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Correlative Light and Electron Microscopic Pediatric Pathology

Previous Serial Number: None

Principal Investigators: Jack H. Carleton, M. D.
Lewis E. Lipkin, M. D.
John L. Priester

Other Investigators: Luz A. Froehlich, M. D.
Toshio Fujikura, M. D.

Cooperating Units: Division of Pediatric Pathology
Department of Pathology
Children's Hospital
Columbus, Ohio

Department of Pathology
Ohio State University
College of Medicine
Columbus, Ohio

Man Years

Total: 1.5
Professional: .9
Others: .6

Project Description:

Objectives: To apply the techniques of preparing large epoxy sections for light and subsequent electron microscopy (developed in our laboratory, Serial No. NDB (CF)-67 PR/P 1518) to a representative number of cases from a medical school with a large pediatric hospital and obstetrical department. These specimens will be used to augment our own PRB pathology material by providing ultrastructural comparisons to conventional histopathology in the areas being investigated by the project and, in addition, will serve as the basis for a possible unique atlas and teaching library of the ultrastructural aspects of pediatric pathology.

Methods Employed: The principal investigator was assigned for temporary duty to the Department of Pathology, Division of Pediatric Pathology, College of Medicine, Ohio State University Hospital, Columbus, Ohio for a six-month period to personally collect at autopsies, surgical procedures and deliveries tissue specimens under the following protocol:

a. A 2 mm thick by 1 cm square (or less) specimen will be secured from all surveyed autopsy tissues which are emendable to inclusion in the ultrastructure pediatric pathology library.

b. A similar sized block of tissue will be obtained from all surgical specimens, biopsies and abortus or miscarriage material when feasible.

c. The tissue will be fixed in veronal buffered 4% gluteraldehyde for five hours, then rinsed and stored in buffer.

d. Specimens were then sent to our electron microscopy laboratory in the PRB Section on Pathology where our chief electron microscopy technician embedded the specimens in large epoxy blocks and sectioned 1 and 8 micron sections from each.

e. One thick and one thin section will be stained with Gallocyanin, mounted in epoxy and filed along with five thin and five thick unstained sections mounted on cover slips for re-embedding procedures.

f. A detailed summary sheet on each specimen will accompany the tissue until all processing data is recorded.

g. An H&E and one unstained paraffin slide was obtained from each original specimen and filed with the plastic embedded sections.

h. Following the completion of collecting and processing of the pathology specimens, selected areas from representative cases will be re-embedded, sectioned and stained for electron microscopy with pre-embedded light micrographs and subsequent electron micrographs being taken for utilization in an atlas on the ultrastructure of pediatric pathology and a unique PRB pediatric pathology ultrastructural library.

It is anticipated that during the six months of collecting pathology specimens, approximately 150 autopsied medical and surgical cases will be processed as outlined. These cases, based on previous accessions, should include an estimated 35% congenital malformations, 20% newborn lesions, 15% primary infections, 10% malignancies, and 20% others.

In addition, approximately one-third of the cases should be newborn or stillbirth autopsies. In cooperation with the Department of Obstetrics and Gynecology, specimens will be collected from all available and pertinent placentas.

Significance to Bio-medical Research and the Program of the Institute: Using our two-staged embedding procedures, an ultrastructural evaluation of pediatric diseases can be accomplished with a magnitude previously unobtainable at a greatly reduced investment of professional time. This submicroscopic investigation of newborn and neonatal pathology will greatly enhance our interpretation of the light microscope findings in our project material and in the pediatric pathology community in general. It will also give us the ability to prepare a unique atlas and teaching library to compare pathology and normal conditions as seen by both light and electron microscopy.

Proposed Course: During 1968-1969 the material obtained will be organized for reference purposes.

Honors and Awards: None

Publications: None

Serial No. NDB-(CF)-68 PR/SLH 1520
1. Perinatal Research Branch
2. Section on Speech, Language and Hearing
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
July 1, 1967 through June 30, 1968

Project Title: Explorative Study for the Use of a Speech and Language Screening Examination for 3-Year Old Children in the Home Situation

Previous Serial Number: NDB-(CF)-63 PR/Bs 1167

Principal Investigator: Dr. Miriam F. Fiedler

Other Investigators: Dr. Eric H. Lenneberg

Cooperating Units: Children's Medical Center, Boston, Massachusetts
Section on Behavioral Sciences, PRB, NINDB
Section on Pediatric-Neurology, PRB, NINDB

Man Years:

Total:	.5
Professional:	.2
Other:	.3

Project Description:

This is the first of two studies to try and determine the most efficient way of identifying those 3-year olds whose speech and language development is atypical and may be associated with neurological and sensory defects. At Boston, the Children's Medical Center has developed a home interview form designed to obtain information on the child's speech, language and hearing from the mother; a comparative study of children whose mothers have been interviewed with this form, and on whom (the children) speech, language and hearing examination results are available, is contemplated. This study is in the final stages of preparation for publication. Dr. Eric H. Lenneberg has replaced Dr. Martin A. Mendelson as an investigator due to Dr. Mendelson's departure from the Project.

Part of the study was presented by Dr. Fiedler as a paper delivered at the Tri-City Meeting of the Obstetrical Society in Boston on May 16, 1967, under the title "Delayed Speech Development in Children at 3 Years of Age Related to Peri- and Postnatal Findings."

Honors and Awards: None

Publications: None

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